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REVIEW

Research progress on prognostic factors of gallbladder carcinoma

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Abstract

Background Gallbladder carcinoma is the most common malignant tumor of the biliary system, and has a poor overall prognosis. Poor prognosis in patients with gallbladder carcinoma is associated with the aggressive nature of the tumor, subtle clinical symptoms, ineffective adjuvant treatment, and lack of reliable biomarkers.

Purpose Therefore, evaluating the prognostic factors of patients with gallbladder carcinoma can help improve diagnostic and treatment methods, allowing for tailored therapies that could benefit patient survival.

Methods This article systematically reviews the factors affecting the prognosis of gallbladder carcinoma, with the aim of evaluating prognostic risk in patients.

Conclusion A comprehensive and in-depth understanding of prognostic indicators affecting patient survival is helpful for assessing patient survival risk and formulating personalized treatment plans.

Keywords Gallbladder carcinoma · Prognosis · Overall survival · Tumor microenvironment · Adjuvant therapy · Biomarkers

Introduction

Gallbladder carcinoma (GBC) is one of the most common malignant tumors of the extrahepatic biliary tract. According to the GLOBOCAN Annual Report in 2020, the number of new GBC cases worldwide is 115,000 (accounting for 0.6% of all cancers), with 84,000 deaths (0.9% of all cancers) (Sung et al. 2021). By 2020, the number of new cases of GBC in China will reach 28,000 (0.63% of all cancers), and the number of deaths will reach 23,000 (0.78% of all cancers) (Sung et al. 2021). Owing to the insidious onset of GBC and lack of typical clinical manifestations in the early stages, most patients are close to the advanced stage when diagnosed, resulting in a loss of opportunity for radical surgery. Therefore, the five-year survival rate is low, at only approximately 5% (Goetze 2015; [Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020; Ma et al. 2023). Even if patients undergo radical surgery for GBC, the recurrence rate is still high, and the prognosis is not ideal (Pandit et al. 2023). Systemic therapies, including conventional chemoradiotherapy and targeted therapy, are ineffective for GBC. Although immune checkpoint inhibitors (ICIs) can achieve good efficacy after improved screening of beneficial patients using gene sequencing and molecular phenotyping, they are limited by their application scope and the occurrence of immune-related adverse events (irAEs) (Guven et al. 2023; Ricci et al. 2020; Rizzo et al. 2023; Rizzo et al. 2021; Sahin et al. 2024). The overall prognosis of GBC has not fundamentally improved. Currently, the eighth edition of the TNM staging system developed by the American Joint Committee on Cancer (AJCC) is widely used in clinical practice. Although TNM staging is useful for prognosis, there are substantial disparities among

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patients with GBC, and it has several limitations (Wang et al. 2020a). In this study, the prognostic factors of patients with GBC were systematically reviewed to provide meaningful references for the comprehensive diagnosis and treatment of patients with GBC (Fig. 1).

Effect of surgical treatment on the prognosis of GBC

Surgery is the only radical treatment for these patients(Cotter et al. 2022). However, differences in surgical methods and procedures can affect the prognosis.

Influence of choice about surgery of different stages on prognosis

According to the latest Chinese Medical Association guidelines for the diagnosis and treatment of GBC, different surgical methods should be adopted for patients with GBC with different degrees of infiltration([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). Simple cholecystectomy is feasible in patients with Tis or stage T1a GBC. For stages T1b and T2a GBC, cholecystectomy combined with wedge resection of the liver tissue > 2 cm from the gallbladder bed is recommended. Cuneiform resection of the liver or the IVb + V segment of the liver is feasible for stage T2b GBC, and the right half of the liver, right trilobectomy, or combined organ resection and vascularization are recommended for stage T3 and above GBC ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). The degree of tumor invasion and surgical scope are controversial (Nag et al. 2021; Tharmalingam et al. 2022). Few studies have been conducted on stage T1b GBC, and the research results vary. A large pathology study on the T1b GBC phase found that in Europe and the United States, the Surveillance, Epidemiology, and End Results (SEER) database was used as a guide; Some studies that included IB cases were incorrectly interpreted as T1b, and pathologic examination was performed without extensive sampling. As a result, the 5-year survival rate of T1b GBC is less than 50%, and additional surgery (radical cholecystectomy) is generally recommended (Pehlivanoglu et al. 2023). However, Chinese and Chilean researchers generally believe that the 5-year survival rate of patients with stage T1b GBC is > 90% and that they can be cured by cholecystectomy (Pehlivanoglu et al. 2023). This study also revealed that of the 11 patients who underwent cholecystectomy and had available peripheral lymph nodes, two were positive for lymph node metastasis, implying that patients with stage T1b GBC are at risk of local progression and that extensive cholecystectomy deserves attention and close follow-up, especially in those with high-risk factors (Pehlivanoglu et al. 2023). This partly explains why the latest Chinese guidelines recommend radical resection of stage T1b GBC combined with liver wedge resection ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). A multinational, multicenter study of patients with stage T2 GBC showed that cholecystectomy combined with hepatectomy resulted in a significant improvement in survival compared to cholecystectomy alone in the entire cohort (Liu and Li 2020). However, subgroup analysis in the T2a and T2b cohorts alone showed no statistical difference in the survival rate, however, it can be interpreted that combined hepatectomy has a slight survival advantage over cholecystectomy alone (Liu and Li 2020). In

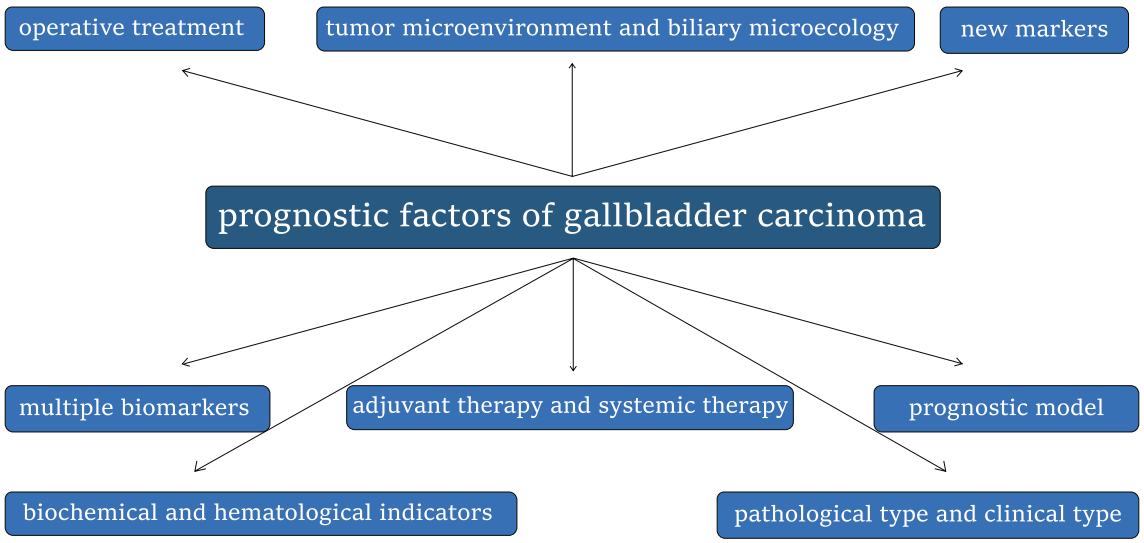

Fig. 1 Prognostic factors of gallbladder carcinoma

addition, in the combined hepatectomy cohort, wedge and IVb + V resection showed comparable survival rates, but the difference was not statistically significant (Liu and Li 2020). Many researchers have also conducted studies on T2 GBC and believe that the survival rate of T2a GBC without hepatectomy is comparable to that of combined hepatectomy with wedge resection, whereas for T2b GBC, combined hepatectomy has significant survival benefits compared with cholecystectomy alone (Jung et al. 2016; Lee et al. 2015; Lee et al. 2017). Studies have also shown that cholecystectomy plus regional lymph node dissection for stage T2a GBC and combined liver wedge resection plus regional lymph node dissection for stage T2b GBC can achieve a satisfactory prognosis without significantly increasing the recurrence rate (Kawahara et al. 2017). Based on these differences, the recommendations of the guidelines should be followed. As wedge resection of the liver does not significantly increase the difficulty of surgery, radical resection combined with liver resection should be routinely performed in patients with T2 GBC. There is no reliable evidence of the efficacy of evidence-based medicine ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). For stage T3 GBC, whether liver segment resection should be performed is also controversial. Yu et al. reported that in patients with suspected stage T3 GBC before surgery, the overall survival rate of radical wedge resection of the liver combined with hepatoduodenal ligament lymph node dissection was similar to that of radical segmental hepatectomy combined with hepatoduodenal ligament lymph node dissection (Yu et al. 2019). Some researchers believe that the survival of stage T3 patients with GBC complicated by liver invasion after radical surgery is less favorable than that after palliative resection (Qu et al. 2012). The latest large-scale cohort study by Chen et al. on patients with stage T3 GBC proposed an improved T3 substage according to the depth and direction of tumor invasion. They conducted a prognostic correlation analysis, and found no statistically significant difference in overall survival (OS) between patients with stage T3a (invasion of the serous membrane without invasion of the liver and a neighboring organ or structure) and stage T3b (invasion of the serous membrane with invasion of a neighboring organ or structure without invasion of the liver) who underwent liver wedge resection and resection of liver segments or more. For patients with stage T3c (invasion of the serous membrane, invasion of the liver, without invasion of a neighboring organ or structure) and stage T3d (invasion of the serous membrane, invasion of the liver, and invasion of a neighboring organ or structure), both of which invade the liver, the OS of patients who underwent liver segment resection or more was significantly higher than that of patients who underwent wedge resection of the liver (Chen et al. 2024) (Fig. 2). Therefore, for T3 GBC without liver invasion, liver wedge resection can achieve a satisfactory prognosis, whereas for T3 GBC with liver invasion, liver segment resection and more should be performed to achieve a satisfactory prognosis (Chen et al. 2024). However, in clinical practice, in addition to macroscopic judgment, preoperative imaging examinations may miss the infiltration of small lesions, and relying solely on pathological examination is not conducive to the implementation of surgery. Therefore, the latest Chinese guidelines suggest that radical surgery based on hepatic segment resection should be performed in patients with stage T3 GBC ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). Most patients with T4 GBC choose palliative surgery or systemic treatment; Few clinical studies have been conducted. For stage T4 (M0) GBC without distant metastasis, performing extended radical surgery combined with organ resection and vascular reconstruction remains controversial. Yuya et al. compared the survival rates of patients with GBC with hilar invasion and those of patients with primary hilar cholangiocarcinoma after radical surgery of the extended right half of the liver and found no statistical difference in the 5-year survival rates (Nasu et al. 2012). Similarly, Lynn et al. found that in patients with GBC and hilar biliary metastasis who were misdiagnosed with hilar cholangiocarcinoma before surgery and underwent radical surgical treatment, the OS was no less than that after radical surgery for hilar cholangiocarcinoma (Nooijen et al. 2023). These studies suggest that aggressive extended radical surgery for T4 GBC with hilar invasion may improve patient survival (Table 1).

Influence of lymph node dissection on prognosis

Currently, the scope of lymph node dissection for radical GBC resection remains controversial, and there is no evidence that lymph node dissection can significantly improve prognosis (Amin et al. 2017; [Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). However, according to the latest TNM staging system of the AJCC, the number of positive lymph nodes detected contributes to the staging of regional lymph nodes ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). The minimum number of lymph nodes to be detected during surgery remains controversial. Narendra et al. found that there was almost no difference in survival rate between N0 and N1 patients based on total lymph node count (TLNC) < 6 during intraoperative dissection, while the survival rate of N0 patients based on TLNC ≥ 6 was better than N1 patients and N0 patients based on TLNC < 6 (Pilgrim et al. 2013). Liu et al. studied the number of lymph node dissection during radical operation of GBC and found that for the overall cohort, the optimal cutoff value was 4, and disease-specific survival (DSS) was worse in the TNLC < 4 group than in the TLNC ≥ 4 group.

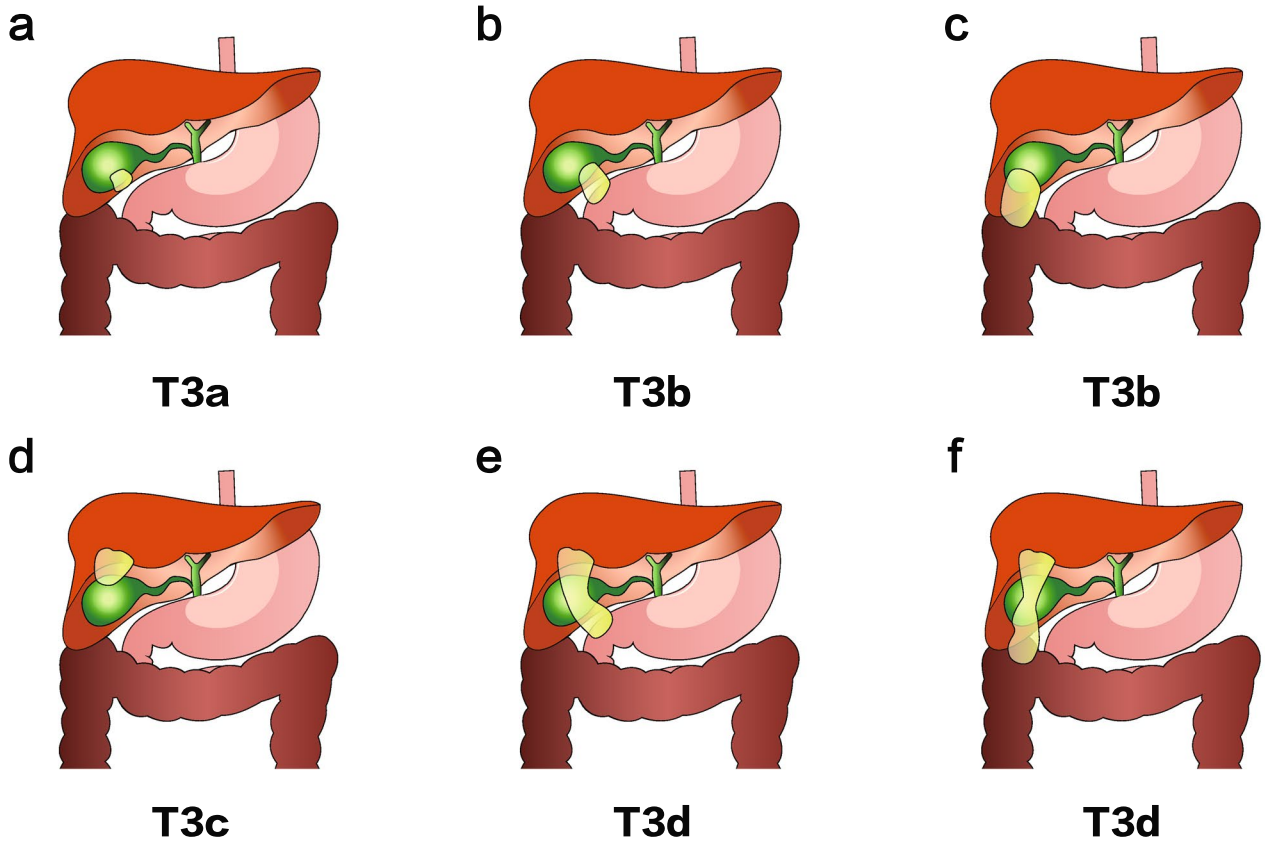

Fig. 2 Improved T3 substage of gallbladder carcinoma. **a** T3a tumor (yellow mass) penetrated the serous membrane without invading the liver or a neighboring organ or structure; **b**, **c** T3b tumor penetrated the serous membrane and invades a neighboring organ or structure, but does not invade the liver; **d** T3c tumor penetrated the serous membrane and invades the liver without invading a neighboring organ or structure; **e**, **f** T3d tumor penetrated the serous membrane and invades the liver and a neighboring organ or structure

In addition, subgroup analysis was conducted on patients with or without positive lymph nodes, and it was found that for patients with positive lymph nodes detected, the DSS in the TLNC ≥ 4 subgroup was significantly better than that in the TLNC < 4 subgroup. Liu et al. also analyzed a positive lymph node group with a TLNC of 6 as the cutoff value. Moreover, its distinguishing ability in these patients seemed to be better than that of TLNC = 4 (Liu et al. 2013). This study also indicates that TLNC is an independent predictor of DSS in GBC (Liu et al. 2013). The latest guidelines recommend that at least six lymph nodes should be detected to adequately stage patients with GBC ([Guideline for the diagnosis and treatment of gallbladder carcinoma (2019 edition)] 2020). However, published studies have generally fallen short of this standard, and in the largest cohort published to date, only 30% of excised specimens had TLNC ≥ 3 (Pandit et al. 2023). Tang et al. compared the effects of different lymph node dissection methods on the lymph node detection rate and prognosis of patients with GBC. Fusion lymph node dissection (group 7, 8, 9, 12 and 13: lymph nodes and peripheral fat, small blood vessels, nerve fusion, as far as possible to complete resection) during radical operation of GBC when compared with standard lymph node (groups 7, 8, 9, 12 and 13:lymph nodes, peripheral fat, small blood vessels and nerves were dissected and cleaned one by one) showed no increase in postoperative adverse events, whereas the total number of detected lymph nodes and the number of positive lymph nodes increased, and the long-term prognosis of patients was improved (Tang et al. 2023).

Influence of application of laparoscopic surgery on prognosis

Since Drouard first described hilar invasion in GBC in 1991, it has been believed that laparoscopic surgery can worsen prognosis, especially if intraoperative complications such as

Table 1 Selection of surgical methods in different degrees of infiltration

T-stage	T-substage	Degree of infiltration	Reference	Conclusion	Suggestion
Tis	Tis	Carcinoma in situ			Simple cholecystectomy
T1	TIa	Invading lamina propria			Simple cholecystectomy
	T1b	Invading the muscle layer	15	there is a risk of progress, at least close follow-up	Radical resection combined with wedge resection of the liver
T2	T2a	The neoplasms on the serosal side invaded the perimuscular connective tissue and did not extend beyond the serosal membrane	16–20	The survival rate of cholecystectomy alone is comparable to that of wedge resection of liver	Radical resection combined with hepatectomy (wedge resection or IVb + V resection)
	T2b	The neoplasms on the hepatic side invaded the perimuscular connective tissue, but did not invade the liver		Hepatectomy combined with cholecystectomy is more beneficial than cholecystectomy alone	
T3	T3a	penetrating the serous membrane without invading the liver or a neighboring organ or structure	21–23	The overall survival rate of liver wedge resection is comparable to that of liver segment and above resection	At a minimum, radical resection based on liver segment (IVb + V segment) should be performed
	T3b	penetrating the serous membrane and invades a neighboring organ or structure, but does not invade the liver			
	T3c	penetrating the serous membrane and invades the liver without invading a neighboring organ or structure		The overall survival rate of liver segment and above resection is better than that of wedge resection	
	T3d	penetrating the serous membrane and invades the liver and a neighboring organ or structure			
T4	T4	Invading the portal vein or main hepatic artery, or directly invading two or more extrahepatic organs or structures	24–25	Extended radical treatment with hilar biliary metastasis results in survival not weaker than radical treatment of primary hilar cholangiocarcinoma	Patients with hilar invasion should be actively treated with extended radical surgery

gallbladder rupture and excessive extension occur (Goetze and Paolucci 2006). Some animal studies have shown that carbon dioxide stimulates tumor growth and enhances tumor implantation associated with peritoneal damage; however, the adverse effects of laparoscopic cholecystectomy (LC) on GBC survival has never been tested in large-scale clinical research (Aoki et al. 1999; Jacobi et al. 1997). Wullstein et al. studied the influence of LC-related complications on prognosis and found that the survival time of patients with LC complications (gallbladder perforation, bile extravasation, and bile duct injury) was significantly shorter than that of patients without these complications and that bile overflow was an independent risk factor affecting the prognosis of GBC (Wullstein et al. 2002). Some researchers have also conducted studies to determine whether LC worsens the prognosis of patients with unexpected GBC (de Aretxabala et al. 2004; Goetze and Paolucci 2006; Sarli et al. 2000; Suzuki et al. 2000). A representative study by Goetze et al. included 377 patients with unexpected GBC, and a stratified analysis was performed according to stage, the result suggested that the survival time after laparoscopic surgery was no less than that after traditional surgery and conversion to laparotomy. Similar conclusions were reached by Xabier and Leopoldo (de Aretxabala et al. 2004; Sarli et al. 2000). Therefore, Suzuki et al. recommended that surgeons maintain reasonable confidence in performing LC even if the lesions are malignant (Suzuki et al. 2000). For patients diagnosed with GBC before surgery, laparoscopic surgery was once considered a restricted area because of concerns about abdominal spread, incisional implantation, and thoroughness of radical tumor treatment. Changwei et al. compared the short-term efficacy and long-term prognosis of laparoscopic and open radical cholecystectomy for GBC and conducted a stratified analysis, excluding the influence of stage; they found that laparoscopic radical operation of GBC could achieve a long-term survival outcome no worse than that of open surgery, and there was no statistical difference in the incidence of complications between the two groups (Dou et al. 2022). These studies suggest that as long as we standardize the intraoperative procedure and accumulate rich experience in laparoscopic surgery, laparoscopic radical surgery for GBC can achieve the same therapeutic effect and prognosis as open surgery.

Influence of second stage radical treatment of incidental GBC on prognosis

The incidence of incidental GBC (IGBC) after LC is 0.2%, which accounts for 5.4% of all cases (Wu et al. 2020). Compared to intraoperative IGBC, the proportion of postoperative IGBC patients undergoing radical surgery is lower because it involves reoperation, which tends to cause greater psychological and physical trauma to patient (Wu et al. 2020). However, patients with IGBC who complete the second-stage radical treatment appear to have a better prognosis. A study that included 84 patients with IGBC found that patients who underwent remedial radical GBC surgery could obtain survival benefits comparable to those who underwent radical GBC surgery simultaneously, and a subgroup analysis found that patients who underwent secondary surgery at an interval of 2–4 weeks had the best prognosis (He et al. 2020). Similarly, Lv et al. compared 110 patients with radically resected incidental GBC (RRIGBC) and 220 patients with primary radically resected GBC (PRGBC) in terms of clinicopathological characteristics and prognosis and found that RRIGBC usually occurred in the earlier stage of the tumor, and the prognosis was better than that of PRGBC (Lv et al. 2023). In contrast to the above studies, many previous studies have reported that the optimal time interval from the initial cholecystectomy to reoperation is 10 days to 2 weeks (Liu et al. 2024a). In a large-scale retrospective analysis conducted by Ethun et al. in 2017, 207 patients with IGBC who underwent re-surgery were divided into three groups based on the time interval between the first cholecystectomy and re-surgery. Patients with an interval of 4–8 weeks had a better median OS than those in the other two groups (Liu et al. 2024a). Currently, the optimal time interval from primary cholecystectomy to reoperation is uncertain, and large-scale multicenter randomized controlled studies are required to guide clinical surgical protocols.

Influence of intraoperative anesthesia on prognosis

The survival rate of patients with tumors is closely related to cellular immunity. Cellular immunity is mainly inhibited by the interactions between the nervous, endocrine, and immune systems (Walter et al. 2012). Immune cells secrete and release various neuropeptide hormones, endocrine hormones, and receptors (endogenous opioid peptides, non-opioid peptides, cortisol, and catecholamines) (Foo et al. 2017; Zen et al. 2010). Surgical anesthesia may be closely related to cellular immunity in the body, and hormones and receptors can inhibit the activity of immune cells, natural killer cells, and humoral immune cells (Li et al. 2015; Pazaitou-Panayiotou et al. 2013). Zhao et al. reported that general or epidural anesthesia affects cellular immunity during surgery, which may lead to tumor recurrence and metastasis by inhibiting immune cell activity, thus affecting prognosis (Zhao and Mo 2015). Zhu et al. conducted a study on patients with GBC based on anesthesia methods and found that epidural anesthesia combined with general anesthesia could reduce intraoperative hemodynamic changes and adverse reactions, improve postoperative cellular immune activity, and be more conducive to the protection of immune function in patients with GBC as well as improve quality of life and survival (Zhu et al. 2017). More large-scale clinical and basic

scientific studies are needed to explore the effect of anesthesia on the prognosis of patients with GBC.

Effect of pathological type and clinical type on prognosis of GBC

Influence of pathological type on prognosis

Adenocarcinoma is the most common histopathological type of GBC. Owing to the small number of cases of the remaining pathological types, most studies on GBC have focused on adenocarcinomas. Gyawali et al. reported a patient with T2bN1M0 gallbladder adenosquamous carcinoma who received no systemic treatment, achieved progression-free survival (PFS) for 2 years, and underwent radical surgery for GBC 2 years later (Gyawali et al. 2023). Li et al. reported a patient with advanced gallbladder squamous cell carcinoma who could not tolerate systemic treatment because of poor systemic condition and only achieved an OS of 2 months (Li et al. 2020). Gera et al. studied bone metastasis of GBC, a rare pathological type, according to data from the SEER database and found that bone metastasis of gallbladder adenocarcinoma was significantly correlated with adverse survival outcomes in patients aged 18–74 years (Gera et al. 2023). Liu et al. conducted a retrospective cohort study of gallbladder neuroendocrine carcinoma (GB-NEC), a rare pathological type, and showed that GB-NEC had a high degree of malignancy. The median OS of the 37 patients was 19 months, and most patients did not undergo radical surgical treatment (Liu et al. 2024b). The rarest histological types of GBC have a high degree of malignancy and poor survival, and only a few cases have reported satisfactory survival results.

Influence of clinical classification on prognosis

In 2019, Zhang et al. retrospectively analyzed the data of 1059 patients who underwent radical resection of GBC from 12 medical centers in China and divided them into abdominal type (I), liver type (II), hilar type (III), and mixed type (IV) according to the tumor growth site and invasion mode. Preliminary results showed that different clinical types were correlated with the TNM stage, biological behavior, and prognosis of malignant tumors (Fig. 3). The proportion of T4 and N1–N2 stages increased stepwise among the four clinical types, and vascular invasion and nerve infiltration were significantly correlated with the clinical type. The median OS of patients with the mixed type is 11 months, which is significantly lower than 48 months with the abdominal type, 21 months for those with the liver type, and 16 months for those with the hilar type (Zhang et al. 2019).

Effects of tumor microenvironment and biliary microecology on prognosis of GBC

It is believed that the occurrence and development of tumors are not only related to the tumor itself but also depend on the complex interactions between tumor cells and their microenvironment. The tumor microenvironment (TME), also known as the tumor stroma, is composed of an extracellular matrix (ECM) and various stromal cells (Quail and Joyce 2013). Changes in TME are closely related to the progression and prognosis of GBC. Simultaneously, the liver and biliary tract are exposed to the gastrointestinal microbiota through the gut-liver axis, and the relationship between changes in the bile microbiome environment and the occurrence and development of biliary tract diseases, especially GBC, has gradually attracted the attention of researchers (Wheatley et al. 2022).

Influence of *cancer*-associated fibroblasts on prognosis

Cancer-associated fibroblasts (CAFs) are key cells in the tumor stroma and the main TME interstitial cells. Studies have shown that CAFs have different gene expression profiles than normal fibroblasts and that they interact with cancer cells through paracrine or autocrine signaling to affect the TME, determine the growth, invasion, metastasis, angiogenesis, and treatment tolerance of cancer cells (Gao et al. 2011; Herrera et al. 2013; Micke and Ostman 2004) and predict the poor prognosis for the patients (Affolter et al. 2013; Johansson et al. 2012). Wang et al. confirmed nicotinamide adenine dinucleotide phosphate oxidase 1 (NOX1) in GBC-associated fibroblasts (GCAFs) expressing α-smooth muscle actin (α-SMA) and fibroblast secreted protein 1(FSP-1) were significantly up-regulated through histopathological examination and cytological experiments in vitro (Wang et al. 2019). In addition, the upregulation of NOX1 expression is related to tumor differentiation, vascular infiltration, and survival rate, and is an independent risk factor for GBC (Wang et al. 2019). Immediately afterwards, Pan et al. performed in vitro and in vivo experiments and verified that GCAFs through the paracrine molecule Interleukin-6 (IL-6)-mediated IL-6 JAK/STAT3 signaling pathway, increase nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX 4) induce the proliferation, invasion, migration, and angiogenesis of GBC cells in vitro and promote the growth and angiogenesis of GBC in vivo (Pan et al. 2020). NOX1 and NOX4 are members of the NOX family, and their main function is to produce reactive oxygen species (ROS), which

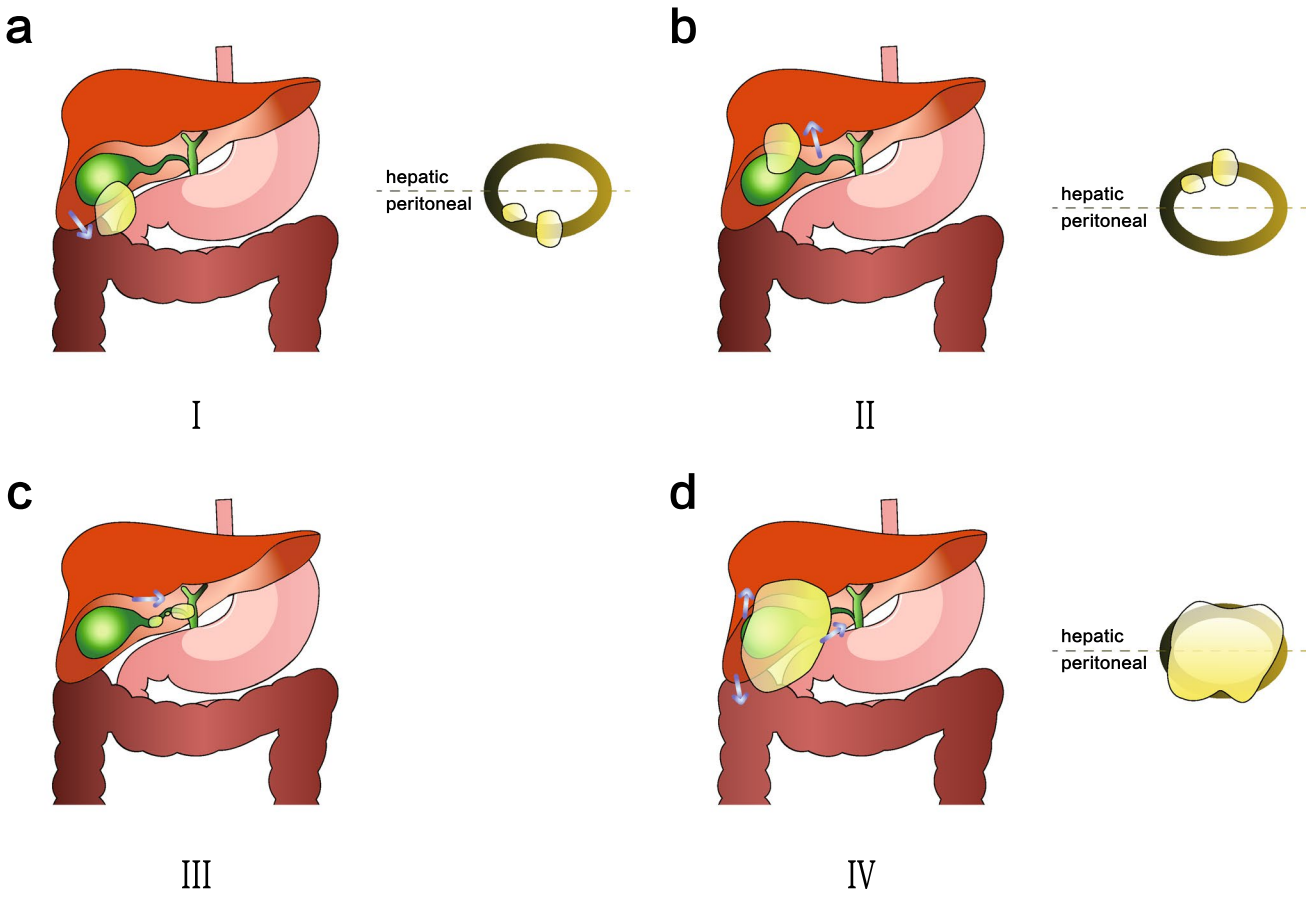

Fig. 3 Clinical classification of gallbladder carcinoma. **a** I abdominal type, tumor (yellow mass) infiltrated to the free side of the abdominal cavity; **b** II liver type, tumor infiltrated to the liver side; **c** III hilar type, Neoplasms of the neck of the gallbladder or tumor infiltrated into the hepatic portal structure; **d** IV mixed type, extensive tumor invasion

are easily converted into oxygen free radicals. Oxidative stress caused by excessive levels of NOX family members is thought to be closely associated with the occurrence of cancer (Altenhöfer et al. 2012; Bartosz 2009; Schröder 2010). GCAFs mediate oxidative stress disorders through the overexpression of NOX family members, which may be an important mechanism promoting the progression and poor prognosis of GBC.

Influence of TME on prognosis

Many reports have shown that GBC combined with acute cholecystitis can increase the risk of intraoperative bile overflow, and that inflammation-induced microenvironmental changes often promote cancer growth (Grivennikov et al. 2010). Using propensity score analysis, Kihara et al. found that the OS and recurrence-free survival of patients with GBC and acute cholecystitis were significantly shorter, indicating that inflammatory infiltration worsens the prognosis of GBC (Kihara et al. 2023). With an increasing understanding of the TME and the rapid development of tumor immunology, the key role of tumor-infiltrating immune cells in the TME has become increasingly clear. Wang et al. built a prognosis model using LASSO regression based on the infiltration intensity of five types of immune cells (macrophages, neutrophils, regulatory T cells (T-regs), cytotoxic T cells, and mast cells) in the GBC microenvironment and found that with an increase in the immune index, the main body of immune cells gradually changed from cytotoxic T cells and mast cells to macrophages, neutrophils, and T-reg cells, and the prognosis deteriorated with changes in immune cells (Wang et al. 2020b). He et al. conducted relevant studies on the heterogeneity of the immune microenvironment of GBC and found that programmed death 1 (PD1), T- cell immunoglobulin domain, and mucin domain 3 (TIM3) in Foxp3 + tumor-infiltrating lymphocytes were significantly correlated with poor patient prognosis. Meanwhile, this study revealed the immunological "cold state" of liver metastasis of GBC lacking immune cell infiltration, further indicating that changes in the immune

microenvironment are closely related to tumor progression and poor prognosis (He et al. 2024).

Influence of biliary microecology on prognosis

The most diverse bacterial community in the human body occurs in the gut, and the human gut flora contributes to the physiological development and maintenance of the host, including education of the host immune system, digestion of nutrients, and defense against colonization by pathogenic microorganisms (Gilbert et al. 2018; Kamada et al. 2013). The gut microbiota is increasingly recognized as an important factor related to tumor development and anticancer treatment effects (Kitamoto et al. 2020; Zitvogel et al. 2018). Bile is considered sterile because of the difficulty in obtaining biological samples; however, recent reports have suggested the presence of a biliary microbial ecosystem in individuals with and without hepatobiliary disease (Molinero et al. 2019; Serra et al. 2021). Additionally, a clinical study using metagenomic analysis showed an association between the carcinogenesis of biliary tract cancer, liver flukes, and the microbiota (Chng et al. 2016). Mari et al. used 16SrRNA sequencing technology to study the composition of bile microbiota in patients with pancreatic cholangiocarcinoma and benign diseases and found that intestinal globules, Staphylococcus, and Bacteroides were factors associated with poor prognosis in biliary malignancies. After adjusting for confounding factors, such as clinicopathological variables, multivariate COX regression analysis showed that the relative abundances of Delftia, Dermococcus, Leucobacter, Methylocapsa, and Staphylococcus were significantly associated with prognosis (Kirishima et al. 2022). This study provides a foundation for the study of bile microorganisms in patients with GBC. Differences in the relative abundance of bacteria directly affect the prognosis of biliary system tumors.

Effect of adjuvant therapy and systemic therapy on prognosis of GBC

Patients with unresectable GBC and those at high-risk of recurrence after radical GBC surgery may benefit from adjuvant therapy. A large cohort study based on the SEER database found that patients receiving adjuvant chemotherapy showed a significant survival advantage compared to those who did not receive adjuvant chemotherapy (Wang et al. 2024b). Studies have also found that adjuvant chemoradiotherapy improves survival to a greater extent than adjuvant chemotherapy in GBC. Subgroup analysis shows that patients who exhibit the following characteristics may benefit more from adjuvant chemoradiation: age ≥ 60 years, female, lymph node positive, tumor size ≥ 5 cm, and no lymph node dissection (Zhu et al. 2023). Although some reports have suggested that preoperative neoadjuvant chemotherapy can successfully achieve conversion therapy in patients with unresectable GBC, most are limited to case reports and lack evidence from large cohorts (Zhang et al. 2023a). Patients with unresectable GBC are typically treated using systemic therapy. In addition to conventional chemoradiotherapy, targeted therapy and ICIs have achieved good efficacy in hematological and other solid tumors; however, there have been no major breakthroughs in their application in malignant tumors of the biliary system (Guo et al. 2022; Liu et al. 2022; Zhang et al. 2023b). Conventional blockers targeting EGFR, FGFR, and other receptors in GBC have been successfully reported, and patients with GBC have achieved long-term survival of nearly five years (De Lorenzo et al. 2021; Sheth et al. 2023). In addition, the application of targeted drugs for receptors such as HER2, TKI, MEK, and BRAF in biliary system malignancies is undergoing clinical research (Goyal et al. 2020; Kim et al. 2020a; Kim et al. 2020b; Lee et al. 2023; Lee et al. 2022; Moehler et al. 2014) (Table 2). Studies have shown that MET, HER2, and EGFR are not only potential therapeutic targets for GBC but also strong prognostic factors for poor prognosis in patients with GBC (De Lorenzo et al. 2021; Kim et al. 2024; Sun et al. 2024). In addition, with expanding research regarding the pathogenesis and biological behavior of GBC, a large number of potential therapeutic targets have emerged, such as targeting MSTIR and downstream genes, which could become therapeutic targets for GBC (Wang et al. 2024a). PD-L1/PD-1 blockers have shown satisfactory results in patients after strict screening (Arkenau et al. 2018; Davis et al. 2022; Klein et al. 2020)(Table 2). Moreover, immunotherapy can achieve better efficacy in patients with high microsatellite instability, high DNA mismatch repair, high tumor mutation load, and high PD-L1 expression. Royal Marsden Hospital Score and Prognostic Nutrition Index are also helpful in screening patients who benefit from ICIs, However, because of the limited use of ICIs, they do not fundamentally change the overall prognosis of patients with GBC (Ricci et al. 2020; Sahin et al. 2024).Furthermore, ICIs-associated irAEs, such as hearing loss, peripheral nerve and sensory lesions, and hypertransaminemia, also restrict their widespread use (Guven et al. 2023; Rizzo et al. 2023; Sahin et al. 2024). In addition, innovative complementary treatments such as cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy reduce the incidence of adverse reactions in advanced GBC and improve survival rates (Wu et al. 2023a).

Table 2 Clinical researches on targeted therapy and immunotherapy for biliary tract tumors

Study, Year	Country	Study Population	Study Design	Sample Size	Treatment Regimen	Targeting receptor	Outcomes	Median Follow up
Targeted therapy								
Choong-Kun Lee, 2023	Korea	phase 2	P, S	34	Trastuzumab plus FOLFOX	HER2	DCR, OS	13 months
Sunyoung Lee, 2022	America	phase 2	P, M	65	Ramucirumab	VEGFR-2	ORR, PFS	10.1 weeks
Lipika Goyal, 2020	America	phase I	P, M	51	DKN-01 plus gemcitabine and cisplatin	Dickkopf-1	ORR, PFS	N/A
Kim et al, 2020b	America	phase 2	P, M	39	Regorafenib	VEGF	PFS, OS	18 months
Kim et al, 2020a	America	Phase 2	P, M	44	trametinib	MEK	PFS, OS	6.6 months
M Moehler, 2014	Germany	phase 2	P, M	102	sorafenib plus gemcitabine	TKI	PFS, OS	11.2 months
Immunotherapy								
Oliver Klein, 2020	Australia	Phase 2	P, M	39	Nivolumab plus Ipilimumab	PD-1/CTLA-4	DCR, PFS	5.7 months
Elizabeth J Davis, 2022	America	Phase 1/2	P, M	87	INCAGN01949	OX40	ORR	N/A
Hendrik-Tobias Arkenau, 2018	United Kingdom	Phase 1	P, M	26	Ramucirumab Plus Pembrolizumab	VEGF/PD-1	ORR, PFS	6.4 months

DCR Disease Control Rate; *M* Multicenter; *OS* Overall Survival; *ORR* Objective Response Rate; *PFS* Progression-Free Survival; *P* prospective; *S* single center

Biochemical and hematological indicators suggest the prognosis of patients with GBC

The use of biochemical and hematological indicators to predict the prognosis of patients with cancer has always been a hot topic in clinical research. There have also been many achievements in the study of GBC, mainly focusing on inflammatory nutritional indicators and other biochemical indicators, such as liver function and coagulation. Wang et al. found that preoperative serum IL-6 levels were significantly correlated with the prognosis of patients with T2 GBC in the liver side. Due to the lack of relevant guidelines for defining patients with high IL-6 levels, this study used the median as the cutoff value for patient stratification, which requires further exploration (Wang et al. 2018). Several studies have shown that inflammatory indicators, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), can be used as prognostic markers for GBC (Cho et al. 2017; Zhang et al. 2015). Previous studies have mostly focused on patients after radical GBC surgery. Choi et al. comprehensively evaluated the prognostic value of the monocyte-to-lymphocyte ratio (MLR), NLR, and PLR in advanced GBC and found that the MLR was an independent prognostic factor for PFS and OS. At most time points, MLR predicted OS better than NLR and PLR (Choi et al. 2019). In addition, some scholars have attempted to combine a variety of indicators to predict the prognosis of patients; for example, Liu et al. found that the NLR (>3.0) and platelet distribution width (PDW >14.76) jointly can be important prognostic markers of GBC and are better than forecast alone (Liu et al. 2024c). Comprehensive scoring systems combining nutritional and inflammatory indicators have been extensively studied. Yang et al. comprehensively evaluated the advantages and disadvantages of several scoring systems and found that, compared with the prognostic nutrition index, controlled nutritional status, and systemic inflammation score, Naples prognostic score consists of serum albumin, total cholesterol, NLR, and lymphocyte-to-monocytes ratio, manifests the largest area under the time-dependent receiver operating characteristic curve and has the best prognostic prediction effect on GBC: the higher the score, the worse the prognosis (Yang et al. 2023). Common clinical blood biochemical indices can also be used as prognostic indicators for GBC. Xu et al. found that alkaline phosphatase (ALP) ≥ 210 U/L and γ-glutamyl transferase (γ-GT) ≥ 43 U/L are prognostic risk factors of GBC. Further

analysis showed that ALP and γ-GT combined with TNM staging could better predict patient prognosis of patients (Xu et al. 2015). In addition, some studies have found that serum D-dimer levels are significantly correlated with the depth of invasion and distant metastasis of GBC, and may be associated with poor patient prognosis (Kong et al. 2021).

Multiple biomarkers to evaluate the prognosis of patients with GBC

With the continuous development of molecular mechanism research in oncology, various biomarkers involved in tumorigenesis and progression have emerged, most of which are related to prognosis. Although the pathogenesis of GBC has not been fully elucidated, some related studies have demonstrated progress, and many prognosis-related biomolecules have been identified that can be used to predict the prognosis of patients or as therapeutic targets.

Traditional biomarkers predict patient prognosis

Traditional biomarkers mainly focus on tumor markers that are commonly used in clinical practice. Sinha et al. showed that the serum levels of CA19-9, CA125, CEA, and CA242 were significantly correlated with GBC, and that CA242 was an independent prognostic factor for GBC (Sinha et al. 2022). In contrast, Kim et al. found that CA19-9 independently predicted survival in patients with GBC, and the conditional reasoning tree method was used for recursion partition-dependent variables based on correlation values to determine the new cutoff value of CA19-9 of 65 IU/ml, demonstrated significantly better predictive power regarding OS than the clinically normal upper limit of 37 IU/ml (Kim et al. 2021b). Wang et al. conducted a similar study and showed that the expression of CA242, CA125, and CA19-9 was of great significance for evaluating lymph node metastasis, monitoring recurrence, and clinical staging of GBC. CA242 is significantly correlated with the early invasion of GBC, and CA19-9 is an independent prognostic factor for GBC (Wang et al. 2014).

Various proteins indicate the prognosis of patients

Studies on the pathogenesis of GBC have identified a variety of proteins related to patient prognosis, mainly focusing on key enzymes related to essential biological functions or metabolism in the human body, as well as key components in important pathways related to GBC. Apurinic-apyrimidinic endonuclease-1 (APEX1) is a rate-limiting enzyme in DNA base excision repair. Proteasome 26S subunit ATPase2 (PSMC2), a member of the 19S regulatory subunit of the 26S proteasome that regulates cell cycle progression, apoptosis, metabolism, and signal transduction, has been confirmed by in vitro and in vivo experiments to promote the progression of GBC and lead to poor prognosis in patients (Wu et al. 2023b; Zhu et al. 2021). Lysine-specific demethylase1 (LSD1) is a type of flavin-dependent monoamine oxidoreductase, which is an epigenetic co-regulator of transcription. One study found that LSD1 promotes the epithelial-mesenchymal transition (EMT), regulates the cell cycle, and promotes GBC cell proliferation and invasion; its overexpression may be a predictor of poor prognosis in GBC (Lian et al. 2015). b1-F1-ATPase (ATP5b) is the β-subunit of H + -ATP synthase, which is the rate-limiting enzyme in mitochondrial oxidative phosphorylation, for which downregulation is generally considered a hallmark of most human cancers. Glutathione peroxidase (GPX) and aldehyde dehydrogenases (ALDHs) participate in regulating oxidative stress and eliminating ROS, cyclo-oxygenase-2 (COX2) is the rate-limiting enzyme in prostaglandin synthesis, which affects cell adhesion, invasion, apoptosis, and immune surveillance. All these factors have been shown to be associated with a poor prognosis of GBC. Negative ATP5b and GPX3 expression, high COX2 expression, and positive ALDH1A3 expression are independent adverse prognostic factors for GBC (Kim et al. 2010; Sun et al. 2015; Yang et al. 2013).

Some key enzymes involved in nutrient metabolism also affect tumor cell growth. UDP-glucose pyrophosphorylase (UGPase) forms UDP-glucose, which is necessary for sugar and polysaccharide synthesis in plants, animals, and bacteria. Wang et al. found that UGP2 can promote the growth of GBC by adjusting the EMT and cell proliferation, resulting in poor prognosis in patients (Wang et al. 2016). Similarly, another study found that phosphoglycerate kinase 1 (PGK1) and pyruvate kinase isoenzyme type M2 (PKM2) are the key enzymes in the process of glucose metabolism, and their expression levels were significantly correlated with a poor prognosis of GBC. Multivariate analysis suggested that low PGK1 expression and PKM2 overexpression were independent risk factors for the prognosis of GBC (Li et al. 2014; Lu et al. 2015). The Hippo pathway negatively regulates the oncogene tumor suppressor pathway, and Yes-associated protein (YAP), the core component of the Hippo pathway, can bind to TEA domain transcription factor (TEAD) and form a YAP-TEAD complex that transcribes multiple oncogenes under the condition of Hippo pathway disorders. Both Kim and Garcia's studies demonstrated that high YAP protein labeling was significantly associated with poorer survival in GBC (García et al. 2020; Kim et al. 2021a) (Fig. 4). In addition, mutational activation of the Ras-Raf-MEK-ERK signaling pathway is frequently observed in GBC, and changes in the expression levels of related proteins, such as Src-homology-2 domain-containing protein tyrosine phosphatase (SHP2), prohibitin (PHB), and epithelial membrane protein 3 (EMP3), have been confirmed to promote the

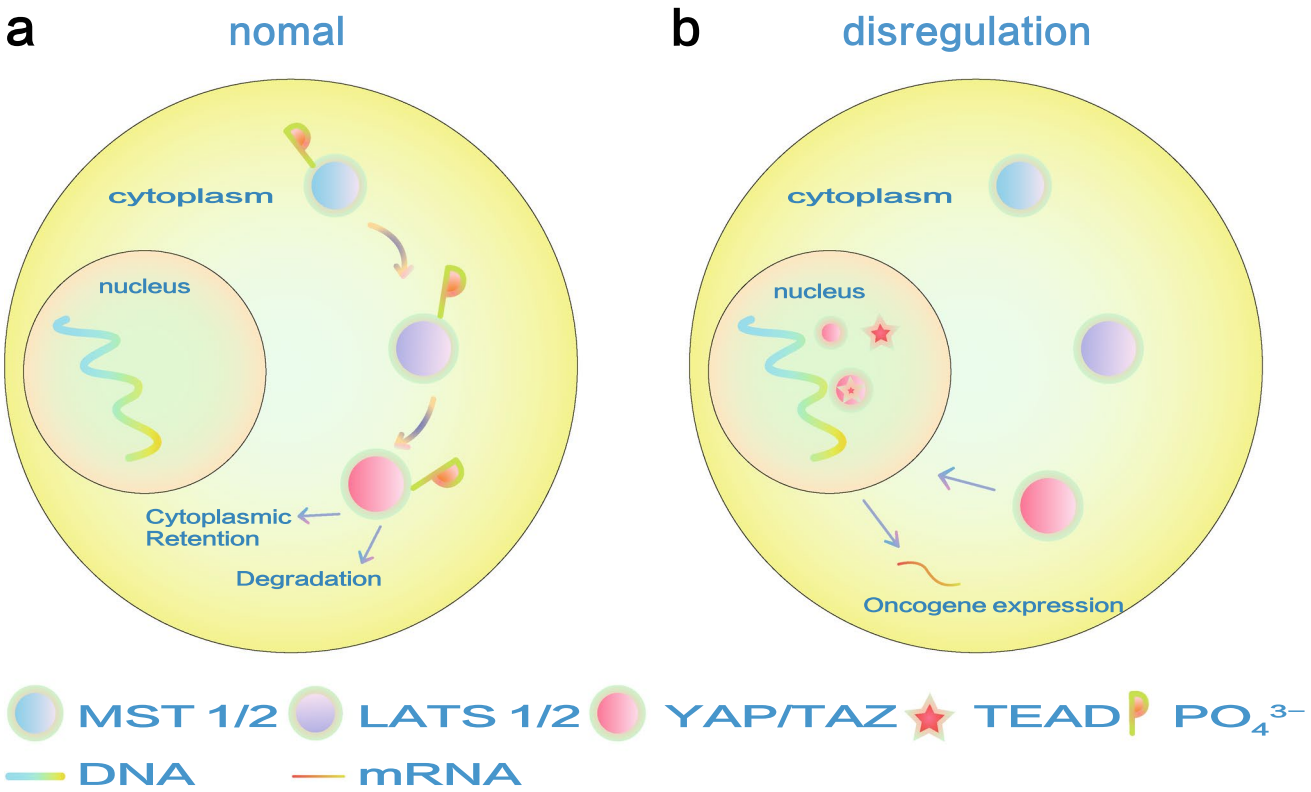

Fig. 4 Hippo pathway in gallbladder carcinoma. **a** When the Hippo pathway is activated, YAP/TAZ activity is inhibited by LATS1/2 mediated phosphorylation and is retained in the cytoplasm; **b** When the Hippo pathway is inactivated, dephosphorylated YAP/TAZ translocates into the nucleus and binds to the transcription factor TEAD1-4 to induce oncogene expression

occurrence and progression of GBC through ERK pathway activation, predicting poor prognosis of patients (Cao et al. 2016; Ma et al. 2023; Wang et al. 2016) (Fig. 5). Proteins, such as vascular endothelial growth factor-C (VEGF-C), eukaryotic translation initiation factor 4 (EIF4E), and chloride intracellular channel 1 (CLIC1), are associated with GBC prognosis and can independently predict survival (Ding et al. 2015; Fang et al. 2019; Jiang et al. 2018; Nigam et al. 2014; Shi et al. 2015) (Table 3).

RNA is associated with prognosis in patients with GBC

microRNA (miRNA) are endogenously expressed non-coding small RNA molecules, primarily functioning to down-regulate gene expression by specifically binding the 3 '-untranslated region of mRNA. It has been widely demonstrated that miRNAs participate in various carcinogenic processes (Jin et al. 2014). Jin et al. observed a significant decrease in miR-34a expression in gallbladder adenocarcinoma tissues and confirmed that forced overexpression of miR-34a can inhibit the colony-forming ability of GBC stem cells and tumor growth in vivo, indicating that low miR-34a is a marker of poor prognosis in patients (Jin et al. 2014). Similar studies have found that patients with low has-miR-372 expression have poorer OS. Previous studies confirmed that CLIC1 is a direct target of has-miR-372, which may be the mechanism underlying the adverse prognosis of GBC (Zhou et al. 2017). In contrast, Yang et al. confirmed that miR-141 was overexpressed in GBC tissues, and the high expression of circulating miR-141 in the blood could predict poor patient prognosis (Yang et al. 2022). In addition, long non-coding RNA (lncRNAs) play an important role in regulating many life activities, such as epigenetics, the cell cycle, and cell differentiation, and they have received increasing attention in oncology. For example, Ma et al. found that patients with GBC with high lncRNAAFAP1-AS1 expression had a poor prognosis (Ma et al. 2016).

Genetic variation and biological behavior affect patient prognosis

Significant geographical and ethnic differences have been observed in the incidence of GBC. This variability can be attributed to environmental exposures and intrinsic genetic susceptibility (Yadav et al. 2018). Kim et al. found that compared to normal tissues, a large number of genes with altered expression were identified in GBC tissues, but few genes were

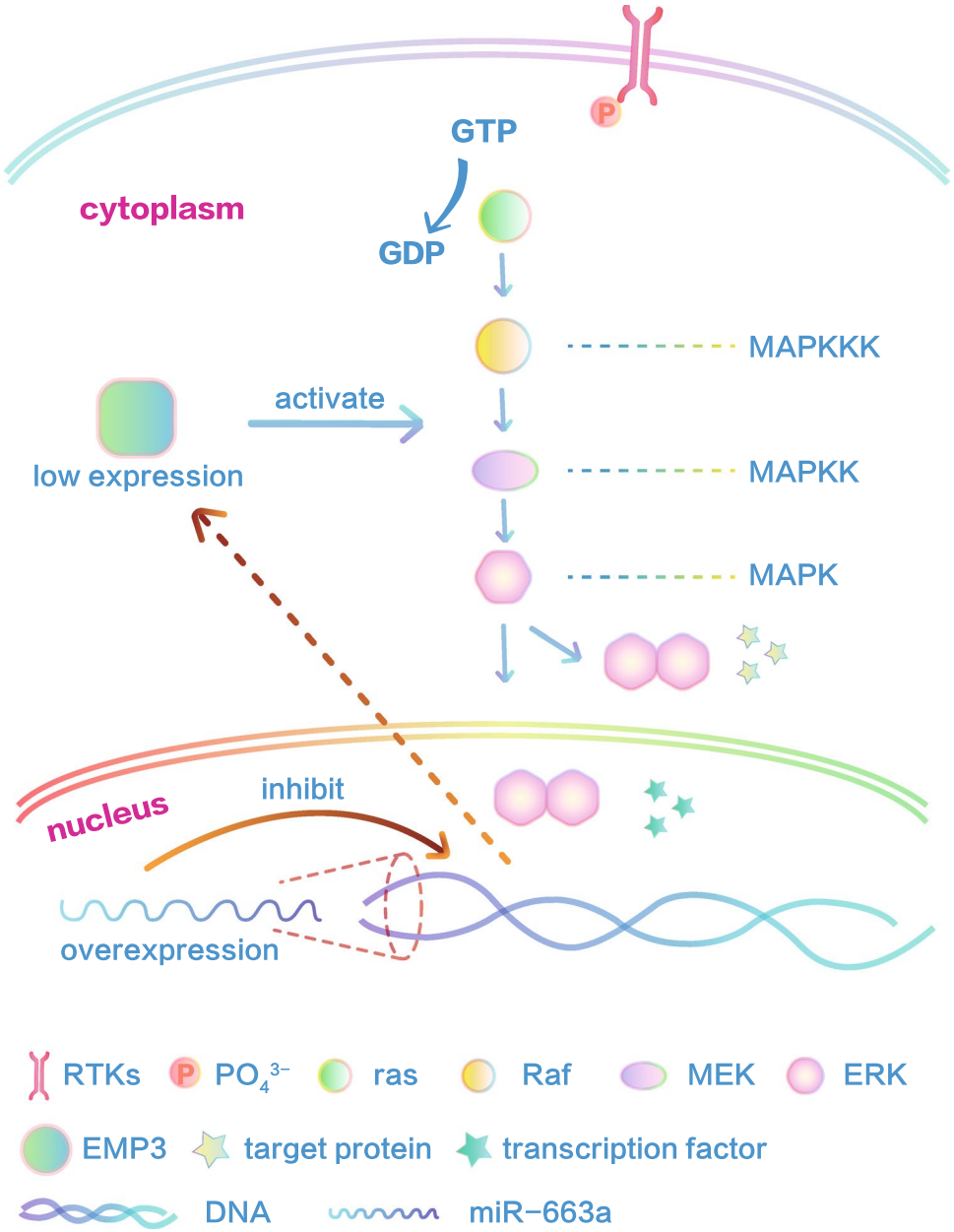

Fig. 5 Ras-Raf-MEK-ERK pathway in gallbladder carcinoma. Overexpression of miR-663a inhibited the translation and expression of EMP3, thereby activating the Ras-Raf-MEK-ERK pathway, and phosphorylated ERK regulates the expression of various transcription factors in the nucleus and promotes gallbladder carcinoma oncogenesis

differentially expressed between the early and late stages, suggesting that most of the gene changes occurred in the precancerous state (Kim et al. 2008). Yadav et al. showed that common genetic variants at the TERT-CLPTM1L and 8q24.21 sites played a role in the susceptibility to and prognosis of GBC (Yadav et al. 2018). Some scholars have also conducted relevant studies on the influence of gene fragments in cancer stem cells on the susceptibility and prognosis of GBC and found that the ALCAMrs1157GA + AA genotype is associated with poor survival in metastatic GBC cases, and the frequency of its polymorphism is significantly correlated with the risk of GBC (Yadav et al. 2016). The malignant biological behavior of GBC is a fundamental cause of poor patient prognosis. Interestingly, KEITA et al. found that in postoperative T2 GBC, the mitotic count (MC) was unrelated to patient survival. However, MC was an independent prognostic factor for T3 GBC. This indicates that rapidly growing early stage GBC may be cured with appropriate surgical treatment, whereas the surgical outcomes for rapidly growing, relatively late-stage GBC may be adversely affected by the malignant biological behavior, resulting in a poor prognosis (Kai et al. 2013).

Table 3 Protein biomarkers that influence the prognosis of gallbladder cancer

Category	Name	Function	Poor prognosis	Reference
Functional correlation	APEX1	Key rate-limiting enzyme in DNA base excision repair pathway	High expression	110
	PSMC2	The 19 S regulatory subunit of 26 S proteasome	High expression	111
	LSD1	Flavin-dependent monoamine oxidoreductase,which is an epigenetic coregulator of transcription	High expression	112
	ATP5b	The β subunit of H + -ATP synthetase	Negative expression	113
	GPX3	Involved in regulating oxidative stress	Negative expression	114
	ALDH1A3	Metabolize endogenous and exogenous aldehydes into carboxylic acids and other active compounds	Positive expression	114
	COX2	A rate-limiting enzyme in prostaglandin synthesis, affecting mitosis, cell adhesion, etc	High expression	115
Metabolic correlation	UGP2	Producing UDP-glucose,which is necessary for the synthesis of polysaccharides by plants, animals and bacteria	High expression	116
	PGK1	Key glycolytic pathway enzymes	Low expression	117
	PKM2	A key enzyme in glucose metabolism, which reflects the metabolic activity of tumor cells	High expression	118
Hippo pathway correlation	YAP	YAP is an important component of the tumor inhibitory pathway that inhibits cell proliferation and promotes cell apoptosis	High expression	119、120
MEK-ERK pathway correlation	SHP2	One of the important pathways in eukaryotic signal transmission network, it regulates the key signaling pathways of cell proliferation, differentiation and apoptosis	High expression	116
	PHB		High expression	121
	EMP3		Low expression	4
Others	VEGF-C	In a variety of malignancies, it leads to lymphangiogenesis and promotes lymph node metastasis	High expression	123
	eIF4E	The hat structure of the 5 'end of mRNA can be specifically identified and plays an important role in the initiation of eukaryotic translation	High expression	122
	CLIC1	It is involved in regulation of cell volume and membrane potential, acidification of organelles, cell cycle regulation, and cell proliferation and differentiation	Positive expression	125

APEX1 Apurine-apyrimidine endonuclease 1; *PSMC2* Proteasome 26S ATPase 2; *LSD1* lysine-specific demethylase-1; *ATP5b* H + -ATP synthetase β subunit; *GPX3* Glutathione peroxidase 3; *ALDH1A3* Aldehyde dehydrogenase-1A3; *COX2* Cyclooxygenase-2; *UGP2* UDP-glucose pyrophosphorylase-2; *PGK1* Phosphoglycerate kinase-1; *PKM2* Pyruvate kinase isoenzyme M2; *YAP* Yes-related protein; *SHP2* Src-homology2 domain protein tyrosine phosphatase; *PHB* Prohibitin; *EMP3* Epithelial membrane protein-3; *VEGF-C* Vascular endothelial growth factor-C; *eIF4E* Eukaryotic translation initiation factor-4E; *CLIC1* Intracellular chloride channel protein-1

Novel markers predict the prognosis of patients with GBC

Sarcopenia is a pathological condition characterized by a reduced muscle mass and body dysfunction owing to various causes (Pedersen and Febbraio 2012; Zeng et al. 2015). Previous studies have shown that sarcopenia is a poor prognostic indicator of gastric cancer, colorectal cancer, and hepatocellular carcinoma (Bozzetti 2017; Reisinger et al. 2015; Sierzega et al. 2019; Voron et al. 2015). Lee et al. reported a significant correlation between sarcopenia and survival in patients with GBC (Lee et al. 2020). Intramuscular adipose tissue content (IMAC) is a novel sarcopenia index. Zheng et al. found that IMAC was an independent predictor of the postoperative prognosis of GBC, and the higher the IMAC, the worse the prognosis (Zheng et al. 2022).

Application of prognostic model in patients with GBC

A common research method is the construction of prognostic models based on various clinicopathological features to guide clinical practice. Survival prediction models for GBC have also been studied extensively. In a representative study, Zhang et al. retrospectively analyzed 1422 patients with non-metastatic GBC in the SEER database and established a GBC-specific survival model based on eight independent risk factors (age, sex, tumor size, histological grade, T stage, N stage, lymph node dissection, and whether chemotherapy was used) to predict the survival rate of patients. This model has higher accuracy and reliability than TNM staging (Zhang et al. 2018). With the application of machine learning and AI algorithms in the field of medical research, predictive models based on the analysis of large-sample data have gradually become widely used.

Based on the clinical data of 122 patients with GBC, Zhou et al. created two multi-index classifiers (MIC1 and MIC2) with high sensitivity and specificity through AI algorithm modeling and combined the avNet and glmnet algorithm models to predict recurrence and survival (Zhou et al. 2023). Cotter et al. investigated a machine learning-based classification and regression tree model, identifying preoperative risk factors for GBC, such as tumor size, preoperative bile duct drainage, serum CA19-9 levels, and NLR; preoperative patients with GBC were divided into four distinct risk groups, with OS ranging from 12.1 to 59.6 months. This helps to identify high-risk patients who may benefit the most from neoadjuvant and adjuvant chemotherapy (Cotter et al. 2022). Interestingly, the prediction models proposed by Choi and Xiao suggest that the log odds of positive lymph nodes (LODDS) can overcome the limitations of the lymph node ratio affected by the number of lymph nodes removed, serving as an independent prognostic factor for GBC. The survival nomogram based on LODDS also demonstrated high performance (Choi and Lee 2020; Xiao et al. 2019). Simultaneously, new data types can be used to build the models. For example, Meng et al. used machine learning to extract the radiomic features of enhanced CT in patients with GBC, applied the DenseNet121 model for deep transfer learning to these radiomic features, and combined it with clinicopathological features to build a hierarchical prognosis model for GBC with good predictive performance. This is helpful for guiding individualized patient treatment (Meng et al. 2023).

Reflection and summary

The biggest factor threatening the survival of patients with GBC is that existing imaging and hematological indicators cannot diagnose GBC early, resulting in most patients missing the best surgical treatment period. Moreover, the pathogenesis and malignant biological behavior of biliary system tumors have not been fully investigated, and their sensitivity to systemic treatment is insufficient, resulting in a poor overall prognosis. However, treatment choice remains controversial. Surgeons must constantly overcome difficulties in surgical treatment. In patients with locally advanced GBC without distant metastasis, radical surgery combined with organ resection and vascular reconstruction may become a treatment method for advanced patients in the future. The combination of multiple anti-tumor drugs has become the main systemic therapeutic method. In addition to chemoradiotherapy, the use of immunotherapy is gradually increasing; however, its application remains subject to many limitations. To help GBC achieve early screening and diagnosis, researchers need to continue to deeply study the pathogenesis of GBC, and explore biomarkers that can change at an early stage, survey a variety of available biological and immunological targets, and promote the research and development of targeted and immunotherapy drugs. Future tumor treatments must include precision therapy—based multi-target combination.

In conclusion, the factors affecting the prognosis of patients with GBC are complex, and some controversial aspects require further evidence-based medical evidence to guide practice. A comprehensive and in-depth understanding of prognostic indicators affecting patient survival is helpful for assessing patient survival risk and formulating personalized treatment plans. With the increase in the number of studies on the pathogenesis of GBC, the prognosis of patients with GBC will gradually improve.

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