Chick *et al. J Cancer Metastasis Treat* 2024;10:22
DOI: 10.20517/2394-4722.2024.47

Journal of Cancer Metastasis and Treatment

Review

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Factors associated with prognosis and staging of intrahepatic cholangiocarcinoma

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How to cite this article: Chick RC, Ruff SM, Pawlik TM. Factors associated with prognosis and staging of intrahepatic cholangiocarcinoma. *J Cancer Metastasis Treat* 2024;10:22. https://dx.doi.org/10.20517/2394-4722.2024.47

Received: 6 May 2024 **First Decision:** 19 Jun 2024 **Revised:** 25 Jun 2024 **Accepted:** 5 Jul 2024 **Published:** 10 Jul 2024

Academic Editor: Ciro Isidoro **Copy Editor:** Fangyuan Liu **Production Editor:** Fangyuan Liu

Abstract

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare but aggressive primary liver cancer with a poor prognosis. A number of established clinical and pathologic factors correlate with prognosis, and this is reflected in the American Joint Committee on Cancer (AJCC) 8th Edition staging manual. Researchers have identified areas for improvement in staging and prognostication of ICC using more nuanced tools, including serum biomarkers, molecular profiling, immunophenotyping, and multimodal prognostic scoring systems. These data have led to proposals of novel staging systems that attempt to improve the correlation between stage and prognosis. More accurate staging tools may aid in treatment decisions that are tailored to each individual patient, to maximize therapy for individuals most likely to benefit and to avoid unnecessary toxicity and decision regret in those for whom aggressive treatment is unlikely to alter outcomes. Artificial intelligence and machine learning may help researchers develop new models that predict outcomes with more accuracy and precision.

Keywords: Intrahepatic cholangiocarcinoma, biliary tract cancer, staging, prognosis, predictive models, machine learning

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a type of biliary tract cancer (BTC) that is a relatively uncommon

aggressive primary liver cancer. Although it shares some similarities with hepatocellular carcinoma (HCC) and extrahepatic cholangiocarcinoma, ICC has unique clinicopathologic, molecular, radiologic, and immune features. The prognosis for ICC is generally poor and increased age, large tumor size, multifocal disease, lymph node metastasis, and vascular invasion are associated with worse overall survival (OS)[1]. The preferred treatment for localized ICC is upfront surgery and adjuvant capecitabine[2-4]. However, even after curative-intent resection, patients are at high risk for recurrence[5]. Chemotherapy, immunotherapy, and targeted therapies are utilized for advanced BTC with variable efficacy[6]. Local therapies, such as stereotactic body radiotherapy, transarterial chemoembolization, or radioembolization, may be used as adjuncts in the advanced setting or for poor operative candidates[3]. The current 8th Edition American Joint Committee on Cancer (AJCC) Cancer Staging Manual uses a tumor-node-metastasis (TNM) staging system for ICC[7]. Although it has evolved over time, the current stages do not always correlate with prognosis[8]. Thus, identification of novel prognostic factors, or refinement of the impact of known prognostic factors, is needed to make treatment decisions for patients with this complex disease.

CLINICOPATHOLOGIC FEATURES

Etiology and patient factors

A variety of risk factors have been identified, including hepatitis B, liver flukes (e.g., *Chlonorchis sensis)*, choledochal cysts, primary sclerosing cholangitis (PSC), hepatolithiasis, and cirrhosis[9]. The prevalence of these risk factors depends heavily on geography, comorbidities, and other individual patient factors. The role of screening among these particular patient populations has not yet been widely adopted but is under active investigation[10]. Interestingly, patients with ICC arising secondary to hepatolithiasis have a worse prognosis but also derive the greatest benefit from adjuvant chemotherapy[11-13]. Data are conflicting regarding the prognosis of hepatitis B-associated ICC relative to other etiologies[14-16]. Malnutrition and frailty are also correlated with inferior outcomes. In particular, sarcopenia has been associated with worse survival outcomes among patients with ICC, including individuals with advanced disease and patients undergoing curative-intent surgery[17,18]. Preoperative nutritional status also impacts survival among patients with ICC. While individuals with lower prognostic nutritional index (PNI) tend to have more aggressive tumor biology with a higher likelihood of multifocal disease, PNI remains an independent predictor of survival on multivariate analysis even after controlling for these factors[19].

The influence of underlying liver disease can be substantial, including younger age, obesity, diabetes, and metabolic-associated liver disease (MALD)[20-24]. Metabolic-associated steatohepatitis, formerly known as nonalcoholic steatohepatitis or NASH, confers a considerably worse prognosis than MALD (previously known as nonalcoholic fatty liver disease or NAFLD); in one study using case-matched cohorts, NASH was present in 22.5% of ICC *vs.* 6.2% in matched cohorts[25]. Cirrhotic patients with ICC have a worse prognosis relative to non-cirrhotic[26,27]. However, combined HCC-ICC has the worst prognosis compared with either HCC or ICC alone, and likely represents a poorly differentiated, aggressive malignancy[28-30]. Higher Albumin-Bilirubin grade (ALBI) predicts improved overall survival[31]. Lower preoperative gamma-glutamyltransferase (GGT) levels are associated with better prognosis among patients with hepatitis B-associated ICC, as well as individuals treated with transarterial chemoembolization[32,33].

Unfortunately, no widely adopted screening guidelines or protocols have been identified/implemented to facilitate early detection of ICC[34]. In turn, many patients present with advanced-stage disease. The impact of the COVID-19 pandemic on access to healthcare highlights the need for early detection; patients diagnosed with ICC during COVID-19 were more likely to present at an advanced stage and had higher mortality compared with pre-pandemic cases[35].

TNM staging

T Category

The AJCC 8th edition staging manual assigns T categories based on tumor size, vascular invasion, number of tumors, and invasion through the liver capsule or into other structures[7]. Multifocal ICC correlates with worse survival, but sometimes it can be unclear if multifocal disease represents a single primary tumor with intrahepatic metastasis, or multiple primary *de novo* tumors arising in a field defect such as cirrhosis or PSC[36]. Central tumors are at higher risk as well; in particular, ICC extending below the second bile duct confluence and those abutting hilar structures have a worse prognosis[37,38]. These factors may influence the likelihood of margin-negative resection. Margin status (positive or negative), as well as the extent of margin width, impacts survival[39-42]. In particular, margins of at least 1 cm confer improved survival compared with margin-negative resection with a width of < 1 cm[39].

Pathologic features

Three distinct growth patterns have been described in ICC: periductal infiltrating, which has been associated with the worst prognosis, *vs.* mass-forming and intraductal growth, which have a better prognosis[43]. The degree of tumor necrosis and the presence of lymphovascular (LVI) and perineural invasion (PNI) also correlate with long-term outcomes[44-46]. Tumor grade and differentiation alone demonstrate a modest correlation with prognosis, but the combination of these factors, termed histologic glandular differentiation, discriminates high-risk from low-risk ICC better than either factor alone[47]. Additional histologic findings continue to emerge, such as the presence of small nerve fibers, sarcomatoid change, degree of lymphangiogenesis, and tumor vascularity, with hypervascular tumors conferring a better prognosis[48-51]. The role of the tumor microbiome is being actively studied in other disease sites and may play a role in the prognosis of ICC as well[52].

N category

Node involvement without distant metastasis represents stage IIIB disease[7]. Lymph node metastases, both on preoperative imaging and final pathologic evaluation, confer a worse prognosis[53,54]. Nodal involvement is classified as Nx, N0, or N1; the presence of three or more involved nodes, or any metastasis to nodes beyond station 12, is associated with a worse prognosis[55].

Performing a lymphadenectomy does not independently improve survival for patients with ICC[56,57]. However, the location and extent of nodal metastases correlate with prognosis, and it is recommended to harvest at least 6 nodes at the time of curative-intent operation for optimal staging[55]. Although 6 nodes have been established as the minimum required for accurate staging, the optimal nodal harvest may be dependent on tumor size. For example, in one study, patients with tumors < 3 cm in size had accurate staging with 7 nodes harvested, whereas individuals with tumors ≥ 3 cm required 11 nodes for accurate staging[58].

Novel staging systems

The AJCC 8th edition remains the primary staging system used in North America. Compared with the 7th edition staging system, the 8th edition performs better relative to prognostic accuracy[59]. Novel staging systems for ICC have been proposed with the goal of improving the correlation between stage and prognosis. One such example is the Clinical Staging system (CS-iCCA) that used the Eastern Cooperative Oncology Group (ECOG) score, number of tumors, tumor size, metastasis, albumin, and carbohydrate antigen 19-9 (CA 19-9) to stratify patients into four stages. This system performed better than the TNM staging system in the derivation cohort, but not in the validation cohort[60]. The MEGNA score incorporated multifocality, extent of tumor, grade, nodal status, and age and performed similarly to the AJCC 8th edition staging system for OS, but not for RFS[61].

SURGICAL FACTORS

Anatomic *vs.* non-anatomic resection

It is unclear if ICC grows along the portal tributaries in a similar way to HCC. As such, the benefit of anatomic *vs.* non-anatomic resection remains controversial. Anatomic resection has been retrospectively compared with non-anatomic resection and conferred survival benefit in a propensity score matched cohort[62]. Another study noted that major hepatectomy, which was correlated with an anatomic resection, was associated with a risk of recurrence[63]. However, this study was not matched using propensity scoring, so the results may reflect the prognostic influence of tumor size rather than the type of resection. Another study suggested that margin width matters more than anatomic *vs.* non-anatomic hepatectomy[64]. These findings should be carefully considered in an era of increasing use of non-anatomic hepatectomy, even for large or multifocal tumors.

Role of minimally invasive hepatectomy

In a nonrandomized study comparing minimally invasive (MIS) to open hepatectomy, MIS was associated with better long-term survival outcomes[65]. Among patients at risk for very early recurrence, minimally invasive surgery was associated with improved long-term outcomes[66]. These data may be related to patients being able to start adjuvant chemotherapy earlier after MIS compared with open hepatectomy. Minimally invasive major hepatectomy is best reserved for high-volume surgeons at high-volume centers[67,68]. Additionally, while debated, some data have suggested that minimally invasive approaches may be less likely to achieve adequate lymphadenectomy[69].

BIOMARKERS

Circulating biomarkers

Serum tumor markers

CA 19-9 is an established serum tumor marker in cholangiocarcinoma. Among patients with ICC, elevated preoperative CA 19-9 can predict lymph node metastasis, early recurrence, and worse overall survival [Table 1][70,71]. In the setting of normal CA 19-9, carcinoembryonic antigen (CEA) may identify a subset of patients at high risk of recurrence[72].

Inflammatory biomarkers

Newer inflammatory biomarker scores, based on values captured during routine laboratory testing, are increasingly incorporated into predictive outcome models for ICC [Table 1]. These biomarkers are rooted in the principle of cancer-related inflammation in which low-level "smoldering" inflammation in the tumor microenvironment (TME) may be associated with progression and metastasis[73]. The neutrophil-to-lymphocyte ratio (NLR) is one such index and has been correlated with ICC prognosis[74-76]. Platelet-to-lymphocyte ratio (PLR) has also been studied among patients with ICC[77,78]. A newer index, termed the systemic immune-inflammation index (SII), is comprised of platelet count multiplied by NLR[79]. In a multi-institutional database study, SII was the strongest prognostic value on multivariate analysis compared with other inflammatory indices. High SII was associated with a 5-year OS of 37.7% *vs.* 46.6% ($P < 0.001$)[79]. These indices have been further combined with nutritional markers. A high fibrinogen-albumin ratio index was associated with reduced RFS[80]. A combination of ALBI, SII, NLR, and prognostic nutritional index, termed the Prognostic Immune-Inflammatory-Nutritional score (PIIN), stratified patients with ICC into low- and high-risk groups relative to OS and RFS[81].

Other immune-related biomarkers have been described, such as nardilysin, a metalloendopeptidase that plays a role in tumor immune response. Nardilysin is intriguing as a measurable serum marker for molecular changes in the TME. High nardilysin levels were correlated with inferior OS and DFS, which was associated with messenger RNA (mRNA) expression in resected ICC specimens[82]. With increasing interest

Table 1. Biomarkers and their correlation with worse prognosis in intrahepatic cholangiocarcinoma

Patient factors	Tumor markers	Inflammatory markers	Somatic mutations	Immune markers
Low ALBI	High CA 19-9	High NLR	TP53	High TMB
Low PNI	High CEA	High PLR	KRAS	Low PD-1/PD-L1
	CTC	High SII	ARID1A	Low TIL
		High nardilysin	BRAF	Low TLS
			FGFR2 fusion	

ALBI: Albumin-bilirubin index; PNI: prognostic nutritional index; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CTC: circulating tumor cells; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune-inflammation index; TMB: tumor mutational burden; PD-1: programmed death receptor 1; PD-L1: programmed death ligand 1; TIL: tumor-infiltrating lymphocytes; TLS: tertiary lymphoid structures.

in molecular detection of cancer in the blood, such as circulating tumor DNA (ctDNA), circulating tumor cell count has been correlated with long-term outcomes in patients with advanced ICC[83]. However, to date, ctDNA has not been well studied in ICC.

Molecular biomarkers

Correlation between driver mutations and disease behavior has been a topic of increased interest across several different cancer types. The molecular phenotype of ICC is variable [Table 1][84]. The most common mutations identified include tumor protein p53 (*TP53*), isocitrate dehydrogenase (*IDH1* and *IDH2*), Kirsten rat sarcoma virus (*KRAS*), AT-rich interactive domain-containing protein 1A (*ARID1A*), hepatocyte growth factor receptor (*C-MET*), V-raf murine sarcoma viral oncogene homolog B (*BRAF*), and fibroblast growth factor receptor 2 (*FGFR2*) fusion[85]. At least one mutation can be identified in about 60% of BTC[86]. Identification of somatic mutations can influence treatment decisions, as the landscape of targeted agents continues to broaden[87].

Somatic mutations that confer the worst overall survival prognosis are *TP53* and *KRAS*. These mutations have been associated with increased tumor mutational burden and advanced stage at diagnosis[88,89]. Co-mutation of *TP53* and *KRAS* is associated with particularly poor prognosis and aggressive biology[90]. ICC with *BRAF* V600E mutation also tends to present at a more advanced stage and has been associated with chemotherapy resistance, though targeted therapies may be an option in the advanced setting[88,91,92]. The presence of *FGFR2* fusion has a variable impact on prognosis, depending on the stage at presentation[93-95]. Multiple inhibitors of the *FGFR2* fusion product have been developed, with generally favorable results in cholangiocarcinoma[96]. A multitude of novel molecular alterations have been described, as the search for druggable targets increases in a tumor-agnostic manner. Dysregulated angiogenesis and neovascularization and epigenetic changes associated with epithelial-to-mesenchymal transition can drive tumor growth and metastasis, and may be amenable to targeted therapies[97-99]. Interestingly, somatic mutations in *IDH1* and *IDH2*, which are components of the tricarboxylic acid cycle, do not influence prognosis independently, implying that there are other metabolism-related changes at the cellular level that may influence tumor biology, such as an interplay between *IDH1/2* and copper- or iron-mediated apoptosis[100-103].

Immune biomarkers

Interest in applying immune therapy to cancers originally thought to be immunologically "cold" has increased dramatically and has been investigated in a biomarker-driven manner[104]. In terms of immunogenicity and sensitivity to immune therapy, cholangiocarcinoma lies somewhere between highly immunogenic tumors such as melanoma and immunologically "cold" tumors such as pancreatic ductal adenocarcinoma. Indeed, several inflammatory-immune markers, as described above, have consistently demonstrated a correlation with disease behavior, response to therapy, and outcomes [Table 1].

Furthermore, immune therapy is now part of first-line standard systemic therapy for advanced biliary tract cancers[6].

Tumor mutational burden (TMB) correlates with poor differentiation, aggressive biology, and immunogenicity, and confers a worse prognosis in ICC[105]. Other molecular features of the TME have been correlated with prognosis, such as the immune checkpoint interaction of programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1). Increased PD-1/PD-L1 expression and the number and type of tumor-infiltrating lymphocytes (TIL) have been demonstrated to confer a better prognosis, whereas decreased TIL and decreased immune checkpoint expression represent an immune-privileged phenotype with a worse prognosis[106-109]. Other immune checkpoints such as B7-H3 have been more recently described and demonstrate a similar relationship with outcomes[110]. In addition to NLR, SII, and other indices, the lymphocyte to C-reactive protein (CRP) ratio may be able to infer immunophenotype based on serum markers[111].

Other components of the TME are important as well. For example, macrophage phenotype, in terms of PD-1 expression, density, and macrophage colony-stimulating factor (M-CSF), correlates with a more immunogenic TME and improved outcomes[112-115]. Tertiary lymphoid structures (TLS) are a marker of immune activation; the number and density in the TME have been correlated with improved survival, demonstrating the crucial role of adaptive immune surveillance in preventing recurrence and metastasis[116-118]. Other markers of immunogenicity that correlate with prognosis include peritumoral plasmacytoid dendritic cells, the chemokine CXCL9, and natural killer (NK) cells[119,120]. Spatial immunophenotyping is a novel and growing method to describe antitumor immunity in a more integrated manner using advanced molecular techniques such as single-cell RNA sequencing. Indeed, the inflamed phenotype has a better prognosis than the immune excluded phenotype, which in turn has a better prognosis than the immune ignored phenotype. These phenotypes correlate with molecular alterations in which the immune excluded and ignored phenotypes were associated with activation of the MAPK pathway, TGF-beta and Wnt/beta-catenin pathways, *BAP1* mutation, and *FGFR2* fusion[121].

The role of cancer-associated fibroblasts (CAF) in the tumor stroma is under active investigation in cholangiocarcinoma as well as other cancers. *In vitro* studies have demonstrated that IL-6 secreted by CAFs prevents autophagy in the TME and allows for tumor growth and immune exclusion[122]. This finding was corroborated in a series of 70 patients with resected ICC in which IL-6 expression correlated with worse prognosis and chemotherapy resistance[123]. This finding may support a role for investigating autophagy-related agents such as resveratrol to treat ICC[124].

As interest in biomarker-driven therapy increases, these immune markers will become increasingly important. An RNA immune signature has been proposed as a predictor of response to chemo-immunotherapy[125,126]. Tumor stemness, based on the expression of *ANO1*, *CD109*, and *CTNND2*, correlates with immunophenotype in which lower stemness is associated with an immune exhausted phenotype with a TME rich in TIL, as well as increased sensitivity to chemotherapy including cisplatin and fluorouracil[127]. A histopathology-based immunoscore, expression of IL23R, and a myeloid-based nomogram originally derived in HCC have also been proposed as immune-related biomarkers[128-130].

IMAGING AND RADIOMICS

Standard imaging techniques

High-quality imaging is essential for the diagnosis and staging of ICC. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound all have a role in diagnosing and staging ICC. Initially

validated in HCC, the Liver Imaging Reporting and Data System (LI-RADS) can be applied to the imaging characteristics of ICC and has been associated with overall prognosis. For example, the LR-M category was independently associated with inferior RFS (HR 8.10, 95%CI: 1.1-58.9), whereas LR-4 and LR-5 were not associated with differences in RFS[131]. Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) is no better at detecting multifocality or macroscopic invasion of vasculature or bile ducts than CT or MRI, but more accurately detects regional lymph node metastasis or distant metastasis[132,133]. A higher metabolic tumor volume on FDG-PET correlates with more aggressive growth and with KRAS mutation status[134].

Radiomics

Given the considerable heterogeneity in the ability of imaging to risk-stratify cholangiocarcinoma, alternative approaches need to be investigated. Radiomics is an evolving area of study based on the use of machine learning to identify radiologic predictors of disease biology[135]. Radiomics may be able to predict early postoperative recurrence risk based on contrast-enhanced CT scans[136]. Pertinent features include tumor shape (e.g., border irregularity or contour) and intralesional heterogeneity[137-140]. Radiomics may also be used to predict features of the TME. In particular, the application of machine learning to MRI was able to identify PD-1/PD-L1 expression[141]. Another study used machine learning and CT imaging to predict the prevalence of tertiary lymphoid structures[142]. As the prevalence of artificial intelligence (AI) increases within medicine and society, these approaches are likely to undergo further study, though their application currently has practical limitations.

PREDICTIVE MODELS

Risk of recurrence

Even in stage I ICC, approximately half of patients will recur; most of these recurrences (85%) occur within 12 months. Risk factors for recurrence in stage I ICC include CEA, SII, tumor size, and omission of lymphadenectomy[5]. Further risk stratification of early-stage ICC is possible using CA 19-9, CEA, tumor size, grade and degree of differentiation, and T stage. Low-risk early-stage patients had an OS of over 5 years and high-risk patients had a median OS of 12 months and a RFS of approximately 6 months[143]. Prognostic risk models may be used to guide adjuvant therapy decisions[4,144]. The Prognostic Recurrence Score (PRS) uses American Society of Anesthesiology classification (1 point), nodal metastasis or unsampled lymph nodes (N1 or Nx, 1 point), margin positive resection (1 point), tumor grade 3 or 4 (1 point), CA 19-9 > 37 at time of recurrence (2 points), CEA > 5 at recurrence (2 points), bilateral recurrence (1 point), and early recurrence (1 point) to quantify risk of recurrence. A PRS score of 3 or greater classifies patients as high-risk, with a median RFS of 36% (compared with 63% in the low-risk group) [Table 2][145].

It is important to identify patients at risk for very early recurrence (VER), defined as recurrence within 6 months of operation. Multiple studies demonstrated poor prognosis among patients with VER[116,146-148]. Without preoperative risk stratification, these patients may be subjected to a high-risk operation that yields little oncologic benefit. As such, a VER score was developed for both the preoperative and postoperative settings. The preoperative score may guide surgical decisions in high-risk patients, and includes age, race, cirrhosis, tumor size, number of lesions, and radiographically apparent nodal metastasis[66]. The postoperative score, which incorporates pathologic information and may be used to influence adjuvant therapy decisions, includes age, race, tumor size, number of tumors, microvascular invasion, nodal stage, and margin status [Table 2][66]. A simpler two-point score was able to predict early recurrence (defined as within 12 months of operation) using the CRP-to-albumin ratio and tumor size greater than 5 cm[149].

Table 2. Validated scoring and staging systems for intrahepatic cholangiocarcinoma, their components, and predicted outcome(s), in order of appearance in the manuscript

Score/system	Patient	Tumor	Node	Metastasis	Biomarkers	Predicts
AJCC8 TNM[7]		Size, number, vascular invasion, extrahepatic invasion	+	+		OS by stage
CS-iCCA[60]	ECOG	Number, size		+	Albumin, CA 19-9	OS by stage
MEGNA[61]	Age	Extent, grade, number	+			OS by stage
Guangzhou[143]		Size, grade, T stage			CA 19-9, CEA	OS, RFS
PRS[145]	ASA	Margins, grade, bilateral at recurrence, DFI	+		CA 19-9, CEA	RFS
VER (Preop)[66]	Age, race, cirrhosis	Size, number	+			Risk of VER
VER (Postop)[66]	Age, race	Size, number, vascular invasion, margins	+			Risk of VER
Chengdu[152]		TBS			CA 19-9, CEA, NLR	
Subtype[153]		TBS			CA 19-9, NLR	OS by common, proliferative, inflammatory subtype
Discordance[155]		Size	+		CEA, NLR	Discordance between preop/postop risk

AJCC: American joint committee on cancer; TNM: tumor node metastasis; OS: overall survival; CS-iCCA: clinical staging-intrahepatic cholangiocarcinoma; ECOG: eastern cooperative oncology group score; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; RFS: recurrence-free survival; PRS: prognostic recurrence score; ASA: American society of anesthesiologists classification; DFI: disease-free interval; VER: very early recurrence; CRP: C-reactive protein; TBS: tumor burden score; NLR: neutrophil-to-lymphocyte ratio.

Multimodality scoring systems

The Tumor Burden Score (TBS) was originally described for HCC, but has been adopted in ICC and CRLM and has been demonstrated to be an independent predictor of prognosis[150]. TBS is calculated with the formula TBS^2 = (maximum tumor size)^2 + (number of tumors)^2[151]. TBS has also been incorporated as a component of other scoring systems. Combining TBS with NLR, CA 19-9, and CEA predicted survival among patients with ICC[152]. When combining TBS with CA 19-9 and NLR, patients with ICC were grouped into common, proliferative, and inflammatory subtypes. The inflammatory subtype had the worst prognosis (median OS 22.9 months) and a higher risk of local and distant recurrence despite lower T and N stages; the common subtype had the best prognosis (median OS 72.0 months)[153]. In a separate analysis of patients with recurrent ICC within a multi-institutional database, hazard function analysis demonstrated that TBS, T stage, and N stage were the strongest predictors of recurrence, and that adjuvant chemotherapy delayed recurrence among individuals with involved or unsampled lymph nodes[154].

An unresolved issue in the assessment of staging and prognosis in ICC is the imprecise correlation between preoperative and postoperative risk assessment tools in surgically resectable patients. In a multi-institutional retrospective study by Moro *et al.*, preoperative variables were used to develop a preoperative prognostic model, and pre- and postoperative variables were used to develop a postoperative prognostic model; these two models were compared to determine the degree of discordance[155]. On multivariate analysis, tumor size, NLR, CEA, and patients with clinically metastatic nodes on preoperative imaging were more likely to have discordance between pre- and postoperative assessment [Table 2]. These findings highlight the need for more accurate preoperative prognostic tools to aid treatment decisions[155].

CONCLUSION

It is difficult to predict prognosis accurately in patients with ICC. Until recently, much of the literature regarding prognostic ICC factors has been limited to a single focus, such as individual clinical or pathologic

factors or particular molecular alterations. The integration of various factors across domains is increasingly used to describe prognosis and propose improvements in staging systems. The use of machine learning in some statistical models, like the random forest model, has been able to identify novel factors that predict early recurrence. The best role for these machine learning models is likely in integrating the most relevant prognostic factors in an accurate and proportional way; in one published machine learning model, the most important prognostic factors to predict early recurrence were TBS, low CA 19-9 (< 200 U/mL), microvascular invasion, perineural invasion, and node-positive or inadequately staged nodal status, all of which are known prognostic factors related to ICC[156]. This role for AI and machine learning continues to evolve, with the goal of identifying the most accurate clinicopathologic factors, serum biomarkers, and molecular/immune factors to predict disease prognosis[157]. Machine learning models may be able to prognosticate and group patients with ICC into more accurate groups based on a multitude of factors[158]. These prediction models are particularly important in terms of guiding therapy decisions when the benefit of high-risk interventions such as hepatectomy and adjuvant chemotherapy may be less clear. Aggressive therapy in patients at high risk for recurrence may increase the risk of decision regret, a source of distress for patients and clinicians alike[159,160]. More data are needed on the relationship between prognostic models, shared decision-making, unfavorable outcomes such as very early recurrence, and decision regret.

The use of large data sets, particularly when informed by AI tools such as natural language processing, may be able to uncover additional prognostic factors or associations that may not be intuitive. There are innumerable factors that could influence disease-specific and treatment outcomes in ICC, some of which may be surprising. For example, patients on calcium channel blockers for cardiovascular indications had improved outcomes compared with those not on these medications[161]. However, novel AI and machine learning tools should be applied with caution, as this approach may be subject to a new set of biases[162].

The studies outlined herein are interesting and thought-provoking, but the practical application of these data, particularly in terms of prognostic calculators and incorporation into widely used staging manuals, is not clearly defined. Multiple studies have demonstrated that a simple TNM classification system is inadequate for ICC[8]. Given that several important prognostic factors are omitted from the TNM system, the incorporation of other factors such as tumor markers, molecular features, immune phenotype, and radiomic data could improve the existing staging systems. This approach has been adopted in breast cancer. For example, the AJCC 8th edition staging manual for breast cancer incorporates hormone receptor status, *ERBB2*/HER2 status, and tumor grade, as well as preoperative and postoperative TNM staging, to provide a more accurate prognosis based on stage[163]. However, it may be prohibitively challenging to incorporate more nuanced techniques such as radiomics and immune phenotypes into staging algorithms that are intended to be universally used. Accurate staging remains a challenge in ICC, evidenced by the variety of available literature. Given the heterogeneity of ICC and the multimodality of prognostic factors, AI and machine learning may assist in synthesizing a coherent and broadly applicable prognostic and staging model.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Chick RC, Ruff SM, Pawlik TM

Availability of data and materials

Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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