Cancer Letters 460 (2019) 10–17

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Coming of a precision era of the staging systems for intrahepatic cholangiocarcinoma?

Zhangjun Cheng[a,b,*], Zhengqing Lei[a,b], Feng Shen[b,**]

[a] Hepato-Pancreato-Biliary Center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, 210009, China
[b] Department of Hepatic Surgery IV, The Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Naval Medical University), Shanghai, 200438, China

ARTICLE INFO

Keywords:
Intrahepatic cholangiocarcinoma
Staging
Prognostic factors
Survival
Precision medicine

ABSTRACT

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer. Appropriate treatment of this aggressive and heterogeneous cancer requires accurate staging and prognostic stratification, as does patient selection for clinical trials. Over the past two decades, several staging systems and prognostic models for ICC have been developed. Most include independent prognostic factors such as tumor extent, clinical parameters and histopathological features and are inaccurate. Accumulating findings offer new insights into the genetic and molecular basis of ICC progression. Hence, staging systems and prognostic models that incorporate in clinicalpathological factors, molecular and genomic information, and tumor biomarkers, and hence more accurately estimate prognosis, will become a reality. This review summarizes the current staging systems and prognostic models for ICC and highlights the need to establish more precise and personalized systems and models that incorporate tumor biologic factors.

1. Background

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, and its incidence had increased worldwide during the past two decades [1,2]. Compared with hepatocellular carcinoma (HCC), ICC is more aggressive with a worse oncological outcome [3]. Even after surgical resection with curative intent, the overall survival (OS) rate of patients with ICC remains dismal [4,5].

Accurate disease staging is critical for selection of proper ICC treatments, prediction of the treatment outcomes, physician-patient communication, and grouping of patients in clinical trials [6]. Over the past two decades, multiple integrated prognostic staging and scoring systems for ICC have been developed. These systems are usually incorporated various independently prognostic factors such as anatomical involvement of ICC, clinical parameters, and histopathological features. In addition, some studies suggest that inclusion of genetic and biomarker information may aid in assigning patients into distinct prognostic groups. In this review, we will highlight the current staging systems and prognostic models for ICC and f the need to develop more precise and personalized systems and models that incorporate tumor biologic factors.

2. Tumor-node-metastasis (TNM) staging systems

Most current TNM staging systems for ICC are based mainly on the anatomic extent of the ICC regardless of clinical factors and tumor biology. Although lymph node involvement (N) and distant metastases (M) are assessed similarly in all TNM staging systems, the definitions in the tumor (T) category vary widely. Most controversial is the prognostic value of the T-classification factors, which include tumor size, tumor number, and serosal invasion.

2.1. The liver cancer study group of Japan (LCSGJ) staging system

The first ICC staging system based on TNM was proposed in 1997 by the LCSGJ [7]. The LCSGJ staging system defined three macroscopic subtypes of ICC: mass-forming, periductal-infiltrating, and intraductal growth. The T-classification factors were tumor size, tumor number and vascular/serosal invasion, while the N- and M − classification factors were similar to those in the American Joint Committee on Cancer (AJCC) TNM staging system [8]. Although used to stage tumors in the LCSGJ staging system, serosal invasion was not independently associated with ICC prognosis in some studies [9–11]. Based on the results of a multivariate analysis of prognosis in 419 patients with ICC who underwent surgical resection, the LCSGJ recently removed hepatic vein

* Corresponding author. Hepato-pancreato-biliary center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, 210009, China.
** Corresponding author.
E-mail addresses: chengzhangjun@seu.edu.cn (Z. Cheng), shenfengehbh@sina.com (F. Shen).

https://doi.org/10.1016/j.canlet.2019.114426
Received 24 January 2019; Received in revised form 2 May 2019; Accepted 4 June 2019

Abbreviations

ICC	intrahepatic cholangiocarcinoma
HCC	hepatocellular carcinoma
OS	overall survival
TNM	Tumor-Node-Metastasis
LCSGJ	Liver Cancer Study Group of Japan
MF	mass-forming
PI	periductal-infiltrating
IG	intraductal growth
AJCC	American Joint Committee on Cancer
JSHBPS	Japanese Society of Hepato-Biliary-Pancreatic Surgery
NCCJ	National Cancer Center of Japan
SEER	Surveillance, Epidemiology, and End Results
EHBH	Eastern Hepatobiliary Surgery Hospital
CEA	carcinoembryonic antigen
CA19-9	carbohydrate antigen19-9
LN	lymph node
LNM	lymph node metastasis
IHD	intrahepatic duct
NLR	neutrophil-to-lymphocyte ratio
PA	pre-albumin
ALP	alkaline phosphatase
TIGER-LC	Thailand Initiative in Genomics and Expression Research for Liver Cancer
PLK1	Polo-like Kinase 1
ECT2	epithelial cell transforming sequence 2 oncogene
CD	cholangiocellular differentiation
FGFR2	fibroblast growth factor receptor 2
IDH	isocitrate dehydrogenase
PTPN3	protein tyrosine phosphatase N3

and serosal invasion from the T category and added portal vein, artery, and major biliary invasion [12] (Table 1). Notably, the analysis linked major biliary invasion to patient survival. The original and revised LCSGJ staging systems have performed well in terms of prognosis stratification in primary cohorts; however, neither has been widely validated or used in countries other than Japan [13,14]. Furthermore, as noted by Sakamoto et al. [12], it is still difficult to differentiate hilar bile duct cancer from ICC involving the hepatic hilum; thus, whether all the participants in their study actually had ICC is unclear.

2.2. The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) staging system

In 2014, the hepatic surgery study group of the JSHBPS assessed the accuracy of the AJCC (7th edition) and LCSGJ staging systems in predicting the survival of ICC patients [15]. Tumor size, tumor number, and vascular invasion were identified as independent risk factors for survival after a curative resection, whereas serosal and periductal invasion were not [15]. Consistent with its previous results [10], the study group found that serosal invasion was not associated with poor prognosis; hence, it was excluded from the T category in the JSHBPS staging system, while a cut-off value of 2 cm for tumor size was retained (Table 1). These changes were incorporated into the revised LCSGJ

Table 1
Overview of The Current TNM staging Systems for Intrahepatic Cholangiocarcinoma.

LCSGJ (2016 by Sakamot et al.)		JSHBPS (2014 by Uenishi et al.)		AJCC 8th edition (2018)
Primary tumor (T)		Primary tumor (T)		Primary tumor (T)
1. Number of tumors	solitary	1. Number of tumors	solitary	**TX** Primary tumor cannot be assessed
2.Tumor size	≤2 cm	2.Tumor size	≤2 cm	**T0** No evidence of primary tumor
3.Vascular or major biliary invasion	vp0, va0, b0-b2	3.Vascular invasion	no	**Tis** Carcinoma in situ (intraductal tumor)
T1 All 3 criteria are fulfilled		**T1** All 3 criteria are fulfilled		**T1a** Solitary tumor ≤5 cm without vascular invasion
T2 Only 2 of the 3 criteria are fulfilled		**T2** Only 2 of the 3 criteria are fulfilled		**T1b** Solitary tumor > 5 cm without vascular invasion
T3 Only 1 of the 3 criteria is fulfilled		**T3** Only 1 of the 3 criteria is fulfilled		**T2** Solitary tumor with vascular invasion or multiple tumors, with or without vascular invasion
T4 None of the 3 criteria are fulfilled		**T4** None of the 3 criteria are fulfilled		**T3** Tumor perforating the visceral peritoneum
				T4 Tumor involving the local extra hepatic structures by direct invasion
Regional Lymph Nodes (N)		Regional Lymph Nodes (N)		Regional Lymph Nodes (N)
N0 No regional lymph node metastasis		**N0** No regional lymph node metastasis		**NX** Regional lymph nodes cannot be assessed
N1 Regional lymph node metastasis present		**N1** Regional lymph node metastasis present		**N0** No regional lymph node metastasis
				N1 Regional lymph node metastasis present
Distant Metastasis (M)		Distant Metastasis (M)		Distant Metastasis (M)
M0 No distant metastasis		**M0** No distant metastasis		**M0** No distant metastasis
M1 Distant metastasis present		**M1** Distant metastasis present		**M1** Distant metastasis present
The LCSGJ staging system		The JSHBPJ staging system		The TNMIS staging system
Stage 0, -		**Stage 0**, -		**Stage 0**, TisN0M0
Stage I, T1N0M0		**Stage I**, T1N0M0		**Stage IA**, T1aN0M0
Stage II, T2N0M0		**Stage II**, T2N0M0		**Stage IB**, T1bN0M0
Stage III, T3N0M0		**Stage III**, T3N0M0		**Stage II**, T2N0M0
Stage IVA, T4N0M0, T1-T3N1M0		**Stage IVA**, T4N0M0, T1-T3N1M0		**Stage IIIA**, T3N0M0
Stage IVB, T4N1M0, Any T Any N M1		**Stage IVB**, T4N1M0, Any T Any N M1		**Stage IIIB**, T4N0M0, Any TN1M0
				Stage IV, Any T Any N M1

Abbreviation: LCSGJ, liver cancer study group of Japan; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; vp0, no portal vein invasion; b0-b2, no biliary invasion or minor biliary invasion within second-order branch of the bile duct.

staging system [12]. Although the JSHBPS staging system was based on data derived from a nationwide study, complete external validations is still lacking.

2.3. The AJCC staging systems

The first independent staging system for ICC in the AJCC TNM staging system (7th edition) was proposed in 2010 [16]. Several ICC-related changes were made in the 8th edition, which was introduced in 2018 [17]. These included the division of the T1 stage into T1a and T1b stages according to tumor size (≤5 vs. > 5 cm), suggesting that tumor size provides distinctive prognostic information. As additional changes, the previous T2a (solitary tumor with vascular invasion) and T2b (multifocal tumor with/without vascular invasion) stages were integrated into the T2 stage, and the T3 stage was divided into the T3 (tumor perforating the visceral peritoneum) and T4 (tumor involving local extrahepatic structures by direct invasion) stages after the tumor growth pattern was excluded from the T category (Table 1).

For N classification, the recovery of at least six lymph nodes from the appropriate nodal stations is recommended by the AJCC (8th edition). Specifically, surgeons must harvest at least six lymph nodes during surgery, and pathologists must examine at least six; otherwise, the evaluation of N status will be inaccurate. Notably, in this edition, the presence of regional lymph node involvement was defined as N1, while all ICCs spreading to the extraregional lymph nodes including the celiac, periaortic, and pericaval lymph nodes were grouped as distant metastatic disease (M1). This indicates that such ICCs have a similar prognosis as those invading distant sites such as the peritoneum, bone, lungs, and pleura; however, the former are usually resectable, while the latter are usually not. Whether placing extraregional lymph node metastasis and distant site metastasis in the same subgroup is appropriate requires further investigation.

Several studies have evaluated the newly proposed AJCC TNM staging system (8th edition) for ICC [18–21]. Most reported that this new edition did not significantly improve overall prognostic stratification. Of note, studies from both the East and West showed that the prognosis of patients with T3 ICC was similar to or better than that of patients with T2 ICC; hence, there was no noticeable prognostic difference between these classifications [19,20]. These results suggest that the 8th edition overestimates the importance of serosal invasion and that appropriate modifications of the ICC stages in this edition is necessary.

2.4. Other staging systems based on TNM classification

In 2001, Okabayashi et al. [22] at the National Cancer Center of Japan (NCCJ) proposed a staging system exclusively for the mass-forming type of ICC. This system defines T1 as a solitary tumor without vascular invasion, T2 as a solitary tumor with vascular invasion, and T3 as multiple tumors. In this system, tumor number rather than tumor size is the primary determinant of survival. Although relatively simple and thus it easy to use in clinical practice, the NCCJ staging system has been criticized for the small number of patients (n = 60) upon which it is based and its poor prognostic applicability [13,14,23].

As reported by Nathan et al. [14], tumor size was not an important predictor of survival in a 2006 analysis of 598 ICC patients derived from the Surveillance, Epidemiology, and End Results (SEER) database. Hence, these investigators modified the AJCC staging system (6th edition) by combining the T2 and T3 categories. The staging system proposed by Nathan et al. [14] was validated by Farges et al. [11] and included in the 7th edition of the AJCC staging system. However, neither the NCCJ or Nathan staging system considered tumor size, which may be inappropriate given the association between tumor size and prognosis in several studies [5, 24-27].

3. Prognostic nomograms

Although TNM categorization enhances our overall understanding of tumor extension, however, it provides limited information about patient-specific prognosis in patients with biliary cancers. Prognostic nomograms are thought to better predict long-term survival in individual patients with various malignancies [28]. They integrate and graphically display the value of the risk factors affecting the patient's prognosis, and thus improve the predictive performance at least in terms of precision [29]. Several nomograms have been established for ICC, all of which may help predict the survival of ICC patients on a personalized basis [30].

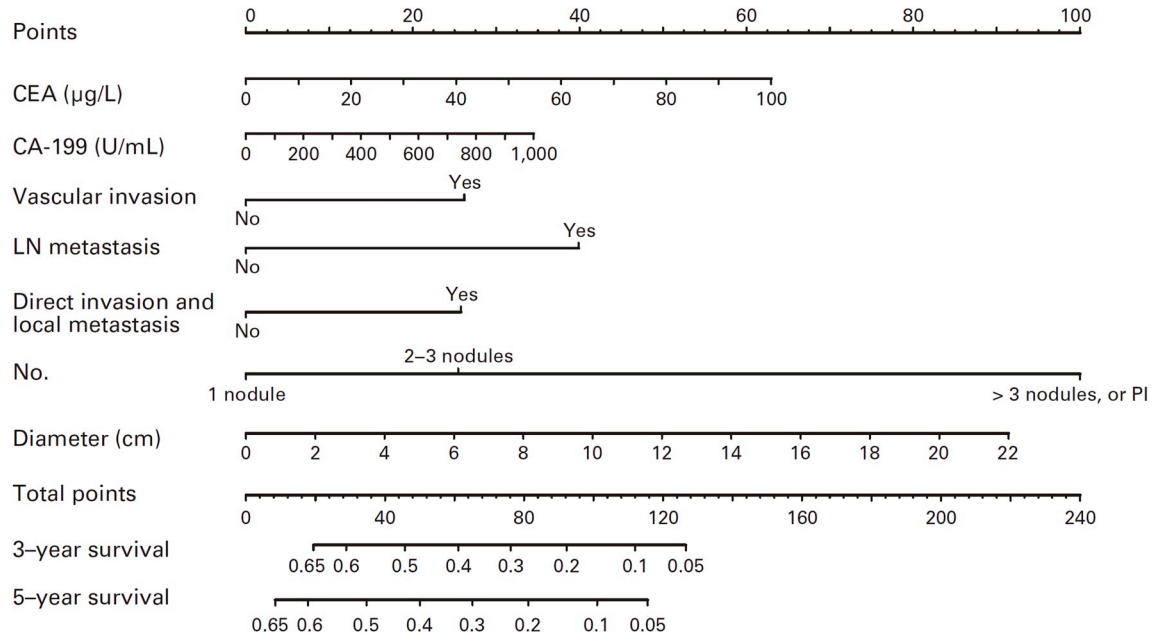

Fig. 1. The Chinese prognostic nomogram for intrahepatic cholangiocarcinoma survival. Cited from Wang et al. [27].
Abbreviations: CEA, carcinoembryonic antigen; CA 19–9, carbohydrate antigen; LN, lymphy node.

3.1. The Chinese nomogram

The first prognostic nomogram for ICC was proposed by Shen and colleagues at the Eastern Hepatobiliary Surgery Hospital in China in 2013 [27]. Predictors included in the Chinese nomogram were serum carcinoembryonic antigen (CEA) level, carbohydrate antigen (CA) 19-9 level, vascular invasion, lymph node metastasis, direct invasion, local metastasis, tumor number and tumor size (Fig. 1 and Table 2). The Chinese nomogram more accurately predicted long-term survival than did conventional staging systems [e.g., AJCC (6th and 7th edition), NCCJ, LCSGJ, and Nathan] and has been validated by several studies (including an institutional study) in both Eastern and Western countris [31,32]. External validation tests confirmed the superiority of the Chinese nomogram over conventional TNM staging systems in terms of predicting the survival of ICC patients [31,32].

Preoperative serum CA19-9 and CEA levels have been independently associated with OS and are thought to play a mechanistic role during metastasis [33–38]. In the 7th edition of its staging system, the AJCC declared that a major challenge to TNM staging is the availability of biological factors that better predict cancer outcomes than does purely anatomical-based staging [16]. Of note, the Chinese nomogram is the first prognostic model for ICC that included serum tumor markers. After the Chinese nomogram was introduced, several studies [26,39,40] demonstrated the importance of tumor markers in ICC staging for estimating survival outcomes. Therefore, efforts are needed to establish a more accurate TNM staging system by incorporating tumor biology factors in the future.

3.2. The Hyder nomogram

Hyder et al. [26] proposed a nomogram for ICC in 2014. In this study, age at diagnosis, tumor size, multiple tumors, cirrhosis, lymph node metastasis, and macrovascular invasion were the factors used to build a prognostic nomogram with a relatively high concordance index of 0.692 (Table 2). The inclusion of age was involved in the predictive model is interesting. Although age is indeed associated with long-term survival in both the normal population and older patients with ICC [33,41], its prognostic usefulness remains controversial. The power of the Hyder nomogram reflects its derivation from the results of a large, multinational, multi-institutional cohort of patients. However, this nomogram does not include serum tumor markers or contiguous organ involvement, which are very important independent prognostic factors for ICC [5,32,33,39,42].

3.3. The Nam nomogram

To date, surgical resection remains the only potentially curative treatment for ICC [43]. Therefore, it is important to stratify patients who is unsuitable for resection according to their preoperative characteristics. Unfortunately, most of the current staging systems and predictive models are mainly based on postoperative factors. Nam et al. [44] recently described a nomogram for preoperatively predicting futile resection in patients undergoing exploration for potentially resectable ICC. Their study identified tumor number, lymph node enlargement, the neutrophil-to-lymphocyte ratio (NLR), and the presence of intrahepatic duct (IHD) stones as independent risk factors for futile resection, all of which were used to generate the nomogram (Table 2). IHD stones and tumor numbers have been associated with poor prognosis [42,45–48]. However, as Nam et al. pointed out, lymph node enlargement is an insensitive indicator of lymph node metastasis, which is widely considered to be an important prognostic factor for ICC [49]. Furthermore, despite the association between an elevated preoperative NLR and poor prognosis in various gastrointestinal malignancies including ICC [50–54], the exact role of the NLR in the prognosis of ICC patients remains unclear. Although further external validation is needed to assess its predictive power, the Nam nomogram nevertheless aids the preoperative selection of patients who will benefit from surgical resection.

4. Prognostic scoring systems

To date, several prognostic scoring systems have been developed. All were established according to total points, with one point assigned to each independent risk factors as identified via multivariable analysis. Most are limited by incomplete inclusion of all prognostic factors. Furthermore, they do not allow patients to be divided into subgroups based on tumor characteristics owing to their lake of generalizability.

4.1. The Zhou score

Zhou et al. [42] proposed a prognostic scoring system for ICC was in 2015. This scoring system was based on an analysis of a cohort at a single institution. Seven independent predictors of OS were included in the scoring system: serum pre-albumin level, serum CA19-9 level, serum CEA level, tumor number, vascular invasion, regional lymphatic metastasis and local extrahepatic metastasis. Patients were then divided into four stages according to the total score: stages I, II, III, and IV, with respective scores of 0, 1, 2–3, and ≥4 (Table 3). The predictors in the Zhou scoring system were more comprehensive than those in the Fudan scoring system, which was published in 2011 [55]. The Fudan scoring system was mainly based on preoperative clinical parameters [e.g., elevated preoperative serum alkaline phosphatase level, elevated preoperative serum CA 19-9 level, multiple tumors, larger tumor size (≥10 cm), and obscure tumor boundary] [55] (Table 3). Although the Zhou scoring system was internally validated in a cohort of 115 patients with ICC, it has not yet been validated by other studies. Furthermore, the prealbumin level, a liver function parameters, is also associated with nutritional status, and its suitability as an independent prognostic factors for OS in ICC patients requires documentation.

4.2. MEGNA score

Recently, Raoof et al. [56] developed and externally validated a prognostic score, named the MEGNA score, using population-based data of ICC patients. In this study, multifocality, extrahepatic extension, higher grade, node positivity, and age > 60 years were independently associated with worse OS. These variables were used to establish the MEGNA scoring system (Table 3), which was then tested in a SEER data set. Unlike other scoring systems, it included tumor grade, which independently and inversely correlates with OS [i.e., high-grade (poorly

Table 2
Summary of the prognostic nomograms for intrahepatic cholangiocarcinoma.

Predictors	Chinese nomogram	Hyder nomogram	Nam nomogram
CEA	0–100 μg/L	–	–
CA19–9	0–1000U/mL	–	–
Vascular invasion	No/Yes	No/Microscopic/ Macroscopic	
Direct invasion/local metastasis	No/Yes	–	–
Tumor numbers	1/2–3/ > 3	Solitary/Multiple	Solitary/ Multiple
Tumor diameter (cm)	0–22	1–15	–
Age (years)	–	55–85	–
Cirrhosis	–	No/Yes	–
Nodal status	–	N0/NX/N1	–
IHD stone	–	–	No/Yes
LN enlargement	–	–	No/Yes
NLR ≥ 2.7	–	–	No/Yes

Abbreviations: CEA, carcinoembryonic antigen; CA 19–9, carbohydrate antigen; IHD, intrahepatic duct; LN, lymph node; NLR, neutrophil-to-lymphocyte ratio; NX, node status cannot be assessed.

Table 3
Summary of the prognostic scoring systems for intrahepatic cholangiocarcinoma.

Variable	Fudan score (0/1)	Zhou score (0/1)	MEGNA score (0/1)
ALP (U/L)	≤147/ > 147	–	–
CA19–9 (μg/L)	≤37/ > 37	≤39/ > 39	–
Tumor number	Solitary/Multiple	Solitary/Multiple	Solitary/ Multiple
Tumor size (cm)	< 10/≥10	–	–
Tumor boundary	Distinct/obscure	–	–
Preoperative albumin (mg/L)	–	< 170/≥170	–
CEA (μg/L)	–	≤10/ > 10	–
Vascular invasion	–	No/Yes	–
LNM	–	No/Yes	No/Yes
Local extrahaptic metastasis	–	No/Yes	No/Yes
Grade	–	–	Low to moderate/High
Age	–	–	≤60/ > 60
Stage (score)	–	–	–
Stage I	0	0	0
Stage II	1	1	1
Stage III	2–3	2–3	2
Stage IV	≥4	≥4	≥3

Abbreviations: ALP, alkaline phosphatase; CA 19–9, carbohydrate antigen; CEA, carcinoembryonic antigen; LNM, lymph node metastasis.

differentiated) tumors have the worst OS rates]. Although the predictive accuracy of the MEGNA score was good in terms of probability of survival, the discrimination index was only modestly improved over that of the AJCC staging system (7th edition, 0.21 *vs.* 0.18) [56]. Moreover, the MEGNA scoring system was based on data derived from a relatively small cohort (n = 275) in the US and has not been validated in other cohorts. Further studies are needed to assess its performance.

5. Molecular subtype

Owing to innovations in molecular biology techniques over the past decade, the progression of ICC is better understood. We now know that the anatomic extent of a disease tells only parts of the story for many cancer patients [17]. In recent years, it has become evident that ICCs are highly heterogeneous, perhaps owing to differences in patient ethnicity, etiology, underlying diseases, tumor microenviroments, the cell of origin, and the genomic and epigenomic changes that drive tumor development [57]. High heterogeneity is responsible in part for diverse tumor biological behaviors and treatment responses, thereby making it difficult to estimate the prognosis and stage of the disease. It also hampers the development of more precise staging and stratification models for ICC [58]. In this context, integration of tumor biological factors, particularly molecular biomarkers, into such models is urgently required for precise, individualized classification of patients.

Via integrated molecular analysis, Sia et al. [59] identified two distinct biological classes of ICC in 2013: an inflammation class with a more favorable outcome, and a proliferation class with a more aggressive clinical behavior. Recently, the Thailand Initiative in Genomics and Expression Research for Liver Cancer Consortium identified common molecular subtypes with a similar prognosis in patients with liver cancer via system integration of genomics, transcriptomics, and metabolomics [60]. The subtypes included C1, which was characterized by mitotic checkpoint anomalies, and C2, which was characterized by obesity, T cell infiltration, and bile acid metabolism [60]. More recently, transcriptomic profiling by Rhee et al. [61] revealed that ICC with cholangiocellular differentiation (CD) resembled an inflammation-related subtype, while ICC without CD resembled a proliferation-related subtype. The authors also identified a CD signature that could predict the prognostic outcomes of ICC, and ICCs were regrouped into G1, G2, and G3 based on the CD signature. This study suggests that combined evaluation of CD histology and protein expression status will facilitate ICC subtyping and the prediction of ICC clinical outcomes [61].

Precise stratification of patients according to tumor heterogeneity requires a complete understanding of the genetic and epigenetic alternations in each subtype [62]. *FGFR2* gene fusions have been detected in ICCs in numerous studies [63–68], and ICCs harboring *FGFR2* gene fusions appear to have distinct clinical and pathologic features, thus defining a unique molecular subtype of ICC with a discrete prognosis [66,68]. Patients with this mutation may benefit from fibroblast growth

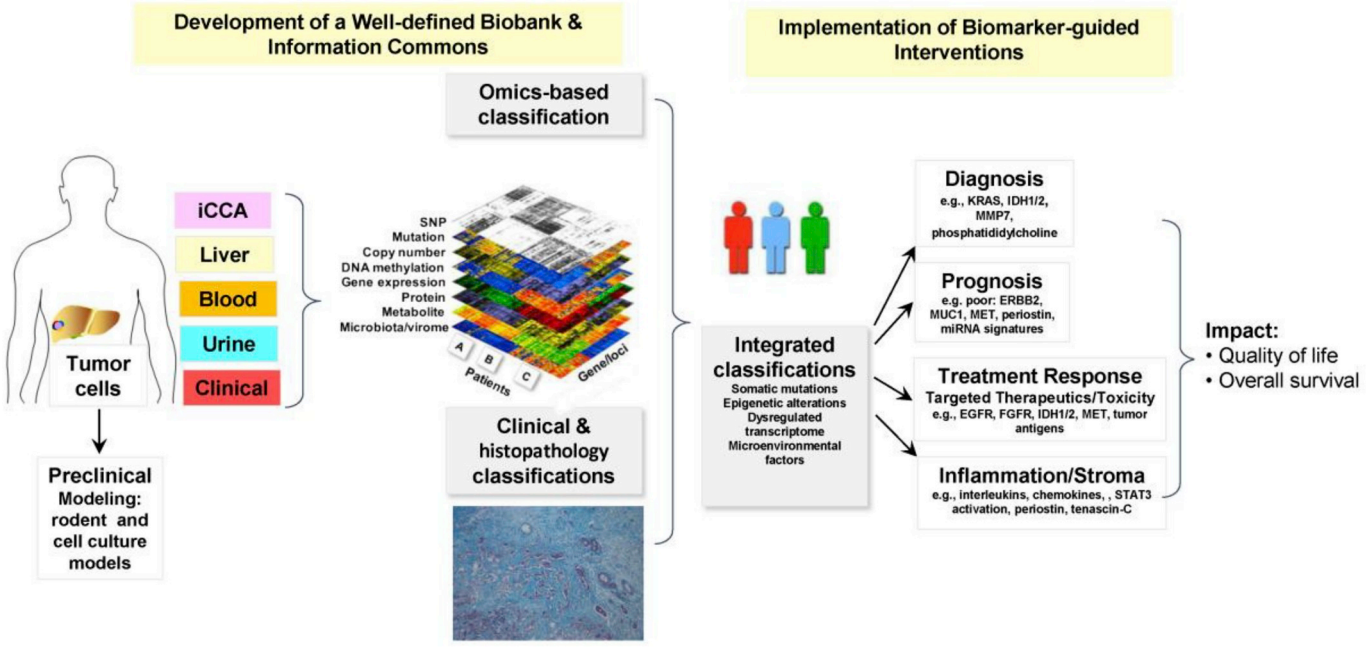

Fig. 2. Schematic depiction of an integrated systems biology-based approach to sub-classifying ICC into distinct subgroups having important clinical implications. for their diagnosis, prognosis, and targeted treatment designs. Cited from Sirica et al. [58].
Abbreviations: iCCA, intrahepatic cholangiocarcinoma; SNP, single nucleotide polymorphism.

factor receptor 2-directed therapy as a personalized clinical approach [62,69]. Various studies observed frequent mutations in *IDH* [70–72], *PTPN3* [73], and some of the genes encoding chromatin-remodeling proteins [74,75] in ICC patients; these mutations correlated with long-term prognosis of patients. Via an integrative analysis, Goeppert et al. [76] identified four major ICC subgroups with widespread genomic and epigenomic differences and prognostic implications. Other studies associated cholangiocarcinomas with upregulated ERBB2 signaling in epithelial cells and concomitant overexpression of inflammatory cytokines (includinginterleukin-6), in the tumor stroma with a highly malignant phenotype [77,78]. Collectively, these results suggest that prognostic stratification should not only be based on the extent of the ICC, but also on the molecular and genetic information of the ICC [79] (Fig. 2).

ICC and HCC differ remarkably from each other in terms of morphology, metastatic potential, and response to treatment. However, some studies suggest that both are derived from hepatocytes [80,81]. Recently, an interesting study by Seehawer et al. [82] demonstrated that a necroptosis-associated, cytokine-rich hepatic microenvironment could switch HCC development to ICC development independently of oncogenic drivers. This finding suggests that ICCs arise in hepatocytes if necroptosis is occurring; hence, such ICCs may differ significantly from those arising in bile duct epithelium.

6. Summary and perspectives

Numerous staging and prognostic models have been developed for risk stratification in ICC. Most of the current staging and classification systems have their own advantages and disadvantages, and there is no a universally accepted system to date. TNM staging and prognostic scoring systems, particularly the AJCC TNM staging system, usually provide general information about the extent of the ICC at initial presentation, which allows us to estimate the prognosis of this disease on a population level. Prognostic nomograms graphically evaluate clinical outcomes and help clinicians preoperatively select patients suitable for curative-intent surgery on an individual basis. However, given the high heterogeneity of ICCs, prognostic modelsthat only include TNM staging and/or clinical factors may not be accurate and require changes to improve the discriminatory power.

As genetic and molecular information about ICC progression accumulates, a precise staging and prognostic models that are based on multiple factors (e.g., clinical background, TNM factors, genomic features, and tumor immune status), and hence are more robust and accurate, will become a reality; however, they will require updating. This goal should be actively pursued in order to better stratify ICC patients for individualized therapy.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding

This study was supported by the Natural Science Foundation of China (grant number 818171988 to C.Z.J.), the Natural Science Foundation of Jiangsu Province (grant number BK20161441 to C.Z.J.), the Six Talent Peaks Project in Jiangsu Province (grant number SWYY-007 to C.Z.J.)

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