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Review

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Advances in post-operative prognostic models for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignancies and a leading cause of cancer-related death worldwide. Surgery remains the primary and most successful therapy option for the treatment of early- and mid-stage HCCs, but the high heterogeneity of HCC renders prognostic prediction challenging. The construction of relevant prognostic models helps to stratify the prognosis of surgically treated patients and guide personalized clinical decision-making, thereby improving patient survival rates. Currently, the prognostic assessment of HCC is based on several commonly used staging systems, such as Tumor-Node-Metastasis (TNM), Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer (BCLC). Given the insufficiency of these staging systems and the aim to improve the accuracy of prognostic prediction, researchers have incorporated further prognostic factors, such as microvascular infiltration, and proposed some new prognostic models for HCC. To provide insights into the prospects of clinical oncology research, this review describes the commonly used HCC staging systems and new models proposed in recent years.

Key words: Hepatocellular carcinoma; Clinical stage; Tumor-Node-Metastasis (TNM); Barcelona Clinic Liver Cancer (BCLC); Nomogram

1 Introduction

Liver cancer is the sixth most frequently diagnosed cancer worldwide, which accounted for approximately 841 000 new cases and 782 000 deaths in 2018 (Bray et al., 2018). China has one of the highest incidence rates of liver cancer on a global scale, with 466 000 new cases of liver cancer and 422 000 deaths in 2015, accounting for approximately half of the total number of cases and deaths worldwide (Chen et al., 2016). Hepatocellular carcinoma (HCC) is the most commonly diagnosed primary liver cancer, which is responsible for approximately 90% of cases (Grandhi et al., 2016). Over the past few decades, strategies for the diagnosis and treatment of HCC have drastically improved. However, HCC is a heterogeneous disease with great variation in the clinical outcomes, resulting in unsatisfactory patient outcomes; the 5-year overall survival (OS) rate of patients with HCC is less than 10% (Grandhi et al., 2016; Wang HB et al., 2019). Hence, it is crucial to establish effective and feasible prognostic models for monitoring HCC patients with poor prognosis and for guiding personalized treatments.

Surgical resection and liver transplantation comprise the first-line treatment modality for patients with early and intermediate stage HCCs; however, the high risk of recurrent metastases severely affects the quality of survival and long-term survival of patients (European Association for the Study of the Liver, 2018; Marrero et al., 2018). To accurately assess the prognosis of patients with HCC for better therapeutic outcomes, researchers have incorporated various prognostic factors into HCC staging systems to increase their reliability and efficiency. More than ten prognostic staging systems, such as Tumor-Node-Metastasis (TNM), Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer (BCLC), have been widely employed in clinical practice; however, no universally

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acknowledged prognostic staging system has been formulated (Borzio et al., 2018; Wang L et al., 2019). The above-mentioned common staging systems incorporate different parameters or focus exclusively on the tumor burden, suggesting that these systems are not inclusive of other important prognostic factors, which limits their accuracy in patient prognosis prediction. To more accurately determine the prognosis of patients with HCC and to develop a universal prognostic model, several studies have evaluated the data of patients undergoing surgical treatment through a rigorous methodology, further incorporating other prognostic factors and validating them in patients from different medical centers. This review describes the currently used prognostic models, including new models that have been proposed in recent years.

2 Clinical staging systems for HCC

As a common practice, following the initial diagnosis of HCC, patients are evaluated using the clinical staging system and are categorized based on the stage of tumor development, to determine subsequent treatment options and to evaluate the efficacy of treatment options such as chemotherapy and immunotherapy. This facilitates the prediction of patient prognoses to a certain extent and speeds up the exchange of information between medical centers. With the advancement of medicine, medical scientists in different parts of the world have developed, revised, and refined various clinical staging systems for HCC for different populations. Despite the efforts of numerous research centers to create a worldwide prognostic scheme for HCC, due to the differences in ethnicity, HCC background, and treatment levels in different regions, the development of a universal clinical staging system has not been accomplished (Table 1) (Tellapuri et al., 2018).

2.1 TNM staging system

The TNM staging, which is a classic clinical staging system, was originally proposed by Pierre DENOIX in 1943 and has been refined by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer. To date, the TNM staging has been updated to the eighth edition that has been applied since 2018 (Amin et al., 2017). TNM staging was established based on the anatomic extent of HCC and was based on primary tumors, regional lymph nodes, and distant metastases. Therefore, TNM staging has good stratification and prognostic value for patients with HCC, especially for those undergoing surgical treatment (Table 2) (Chun et al., 2018).

Based on the results of two clinical studies at the level of evidence II/III, the new TNM staging system consists of a revised primary tumor (T) classification at the seventh stage: the former T1 was divided into T1a and T1b; patients with isolated tumors of >2 cm in diameter and with vascular invasion were classified as T2; and the old T3b was classified as T4 (Chan et al., 2013; Shindoh et al., 2013). Kamarajah et al. (2018) retrospectively included 8918 patients with HCC who underwent hepatic resection or liver transplantation from the Surveillance, Epidemiology, and End Results (SEER) database. They found that the *C*-index of the eighth edition staging (0.60) was slightly higher than that of the seventh edition (0.59), indicating that the eighth edition staging system continues to have good prognostic power for patients undergoing surgical treatment. The study further pointed out that the survival rates for >2 cm single tumors with vascular invasion are better than those for <5 cm multiple tumors. In addition, the prognosis of patients with multiple tumors measuring ≤5 cm in diameter without vascular invasion is better than that of patients with vascular invasion. This suggests that the eighth edition of the T2 classification may need further refinement.

Chen et al. (2021) retrospectively enrolled 37 062 patients with HCC in the Taiwan Cancer Registry (TCR) between 2007 and 2013, and found that the Akaike information criterion (AIC) of the eighth edition staging system (0) was lower than that of the BCLC staging system (353.832) in predicting the OS. This demonstrated the good prognostic ability of TNM staging. In addition, Park et al. (2020) retrospectively analyzed 1008 patients with HCC undergoing radical resection, and found that the area under the receiver operating characteristic (ROC) curve (AUC) values for predicting the 2-year recurrence-free survival and 2-year OS were similar for both the eighth edition and the seventh edition staging systems (0.690 vs. 0.693 and 0.765 vs. 0.770, respectively). However, in contrast to the results of Shindoh et al. (2013) and Zhang et al. (2018), Park et al. (2020) found that, for patients with solitary tumors of ≤2 cm (T1a), patients with vascular invasion had lower OS than those without vascular invasion. Therefore, it needs to be verified whether a

Table 1 Comparison of different clinical staging systems for HCC

Staging system	Year	Advantage	Disadvantage
TNM	1943	Good stratification and prognostic values for surgically treated patients	Over-reliance on anatomical indicators, partial T classification to be verified; does not consider other factors (PS score and ECOG score)
Okuda	1985	Simple and easy to use, with wide applicability	Excessive heterogeneity of patients in Okuda stage II; does not consider late prognostic factors such as vascular invasion and tumor number
CLIP	1998	Well validated, with good identification and prognostic abilities	Cannot effectively differentiate between subgroups 4–6; tumor morphology criteria are too general; most patients are classified as CLIP 1 and CLIP 2; poor stratification ability
BCLC*	1999	Combination of prognostic classification and treatment options into one; widely used clinically (especially in Western countries)	BCLC-stage B is too heterogeneous, with wide variation in therapeutic efficacies; BCLC-stage C does not identify patient homogeneity, and treatment options need to be improved
CNLC	2001	Objective and easy to access data; more suitable for Chinese patients	Applicability to areas outside China needs further study
CUPI	2002	Well validated with strong prognostic performance in patients with HBV-related HCC and equally applicable to Western populations	Unsatisfactory prognostic performance for patients undergoing radical treatment
JIS	2003	Good layering capacity and prognostic performance	Some parameters are more subjective and need to be improved; applicability to western populations needs further study
HKLC	2014	Improves on the shortcomings of the original BCLC staging system and recommends more aggressive treatment, especially for HBV-related HCC endemic areas	Does not appear to provide better predictive value of outcomes than BCLC staging for Western populations; applicability to Western countries needs further validation
ITA.LI.CA	2016	Strong prognostic assessment capability, initially showing broad applicability to European and some Asian patients	Stability and applicability need further validation, especially in areas where HBV-associated HCC is endemic

HCC: hepatocellular carcinoma; TNM: Tumor-Node-Metastasis; PS: performance status; ECOG: Eastern Cooperative Oncology Group; CLIP: Cancer of the Liver Italian Program; BCLC: Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer; CUPI: Chinese University Prognostic Index; HBV: hepatitis B virus; JIS: Japanese Integrated Staging; HKLC: Hong Kong Liver Cancer; ITA.LI.CA: Italian Liver Cancer. * The 2018 version of BCLC staging.

Table 2 Tumor-Node-Metastasis (TNM) classification*

TNM stage	Tumor	Metastatic lymph nodes	Distant metastases
IA	Single tumor ⩽2 cm in diameter (T1a)	No	No
IB	Single tumor >2 cm in diameter without vascular invasion (T1b)	No	No
II	Single tumor >2 cm in diameter with vascular invasion (T2)	No	No
	Multiple tumors, none >5 cm in diameter (T2)		
IIIA	Multiple tumors, any >5 cm in diameter (T3)	No	No
IIIB	Tumor involves a major branch of the portal vein or hepatic vein (T4)	No	No
	Tumor directly invades adjacent organs other than the gallbladder or perforates the peritoneum (T4)	No	No
IVA	Any tumor	Yes	No
IVB	Any tumor	Any	Yes

* The eighth version. Data source: Amin et al., 2017.

further refinement of T1a is needed. Notably, TNM staging relies mainly on anatomical indicators, but it does not take into account factors such as liver function and the patient's general condition (e.g.,

performance status (PS) score and Eastern Cooperative Oncology Group (ECOG) score). Furthermore, some T-classifications that are subject to further validation do not provide appropriate treatment advice, which may affect the accuracy of prediction and the application of staging.

2.2 BCLC staging system

Given the shortcomings of TNM staging, researchers have successively proposed improved staging systems, such as BCLC staging that was proposed in 1999 and is currently the most widely used clinical system for predicting the prognosis of HCC (Table 3) (European Association for the Study of the Liver, 2018). Unlike other staging systems, BCLC staging combines the tumor burden, liver function, and physical status to classify patients (stages 0, A, B, C, and D), and combines prognostic classification and treatment options that are important for the management of HCC. Although the 2018 version of the BCLC staging system has been recognized by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases and is widely used in the West, controversies regarding BCLC stages B and C exist (Kulik and El-Serag, 2019). The 2018 version of BCLC staging system defines stage B as asymptomatic multinodular tumors (multinodular; Child-Pugh: A-B; performance status (PS): 0) and recommends transcatheter arterial chemoembolization (TACE) as the preferred treatment option, but this classification has been challenged. Many studies have pointed out that BCLC-B patients are highly heterogeneous, and it is necessary to classify this group, such as by Bolondi's subclassification, Wada's subclassification, and Kim's substages (Bolondi et al., 2012; Giannini et al., 2016; Wada et al., 2016; Kim et al., 2017). In terms of treatment, the current research points out that the surgical treatment of some BCLC B substages can further extend the survival time of patients (Hou et al., 2016; di Sandro et al., 2019; Zhang ZH et al., 2019).

Another aspect of controversy in the 2018 version of BCLC staging system is stage C (patients with portal invasion/extrahepatic spread (EHS); Child-Pugh: A-B; PS: 1 and 2). Sinn et al. (2015) subdivided BCLC stage C into four substages C1–C4 based on portal vein thrombosis (PVT) and EHS. Jun et al. (2017) subdivided BCLC stage C into five substages (C0–C4) based on tumor size, distant metastasis, HCC type, and bile duct invasion. In a recent retrospective study of 835 patients with BCLC stage C, the investigators classified patients according to their clinical characteristics (PS 1, PS 2, macrovascular invasion (MVI), EHS, and MVI+EHS) and found significant differences in the median OS (Giannini et al., 2018).

In December 2021, Reig et al. (2022) gave a major update to the BCLC staging and released the latest version, that is, the 2022 version of the BCLC staging. Different from the old version, the new BCLC staging incorporates albumin-bilirubin (ALBI) grade, α fetoprotein (AFP) level, Child-Pugh, and model for end-stage liver disease (MELD) scores as indicators to assess the liver functional reserve or compensation. In terms of staging, the new staging divides the most heterogeneous B stage into three subgroups. In terms of staging the treatment plan recommendation, the new BCLC model no longer adopts the previous single treatment method but provides multiple treatment options. It is worth noting that two important treatment concepts are presented in the 2022 version of BCLC staging: treatment stage migration and untreatable progression. Treatment staging migration is used to consider advanced staging treatment modalities when specific circumstance of the patient requires switching recommendation options, and in some cases even a shift from early initial treatment recommendation to late treatment recommendation or even no treatment. Untreatable progression represents the failure of previously selected treatment regimens. In addition, the new BCLC strategy points to the need to stratify the

Table 3 Barcelona Clinic Liver Cancer (BCLC) classification*

BCLC stage	Tumor	Liver function	Performance status	Treatment
Very early stage (0)	Single tumor <2 cm	Preserved	PS 0	Ablation/resection
Early stage (A)	Solitary	Preserved	PS 0	Resection/transplant
	2 or 3 nodules <3 cm	Preserved	PS 0	Transplant/ablation
Intermediate stage (B)	Multinodular	Preserved	PS 0	Chemoembolization
Advanced stage (C)	Portal invasion/extrahepatic spread	Preserved	PS 1 and 2	Systemic therapy
Terminal stage (D)	Not transplantable	End-stage	PS 3 and 4	Best support care

PS: performance status. * Data source: European Association for the Study of the Liver (2018).

progression patterns of patients with tumor progression and engage in a multidisciplinary collaborative discussion to develop the best approach. At present, the view that liver resection has a higher long-term survival rate than TACE for a number of specific BCLC stages B and C patients has been accepted by most scholars, but the new BCLC model does not adopt this view (Zhong et al., 2014; Zhang ZH et al., 2019). Besides, the accuracy and stability of the 2022 version of BCLC staging for prognosis prediction need to be further verified.

2.3 Italian Liver Cancer (ITA.LI.CA) staging system

The ITA.LI.CA staging system is a new prognostic system for HCC proposed by Farinati et al. (2016), which incorporates the ITA.LI.CA tumor staging (stages 0, A, B1–3, and C), the ECOG physical status score (PST), the Child-Pugh score (CPS), and AFP into the prognostic system (Tables 4 and 5) (Parikh and Singal, 2016). The ITA.LI.CA system was derived from a retrospective study of 5183 patients with HCC from the ITA.LI.CA database and was externally validated in 2651 patients from Taiwan, China. The results showed that the prognostic power of this system is significantly better than those of BCLC staging, CLIP staging, Japanese Integrated Staging (JIS), model to estimate survival in ambulatory HCC patients (MESIAH) score, and Hong Kong Liver Cancer (HKLC) staging (Farinati et al., 2016). Borzio et al. (2018) externally validated the ITA.LI.CA system on a cohort of 1508 Italian patients with HCC and obtained the same results. In addition, it was found that the ITA.LI.CA system continued to perform better than the other five prognostic systems, even after patient stratification by radical and palliative treatment. The study further indicated that the ITA.LI.CA system shows the best prognostic performance for patients with HCC who have received the first treatment and were restaging. Moreover, the ITA.LI.CA group also considered other variables (model for end-stage liver disease (MELD) response to first treatment and subsequent treatment) and established a new ITA.LI.CA restaging model to improve the prognosis assessment of patients (Vitale et al., 2018).

2.4 Other staging systems used in Western countries

The Okuda staging system, which was the first system to combine tumor status with liver function, consists of the following four indicators: tumor size, ascites, albumin, and bilirubin. According to this staing system, patients are categorized into three stages (stages I, II, and III). It is a widely used staging system because of its simplicity and ease of application (Table 4) (Okuda et al., 1984). However, due to the high prognostic heterogeneity of patients in stage II of the Okuda staging system, the CLIP study group has expanded on it and proposed further CLIP stages in an attempt to circumvent this problem (The Cancer of the Liver Italian Program (CLIP) investigators, 1998). The CLIP staging system consists of the following four indicators: Child-Pugh staging, tumor morphology, AFP, and PVT. This system was derived by a retrospective study of 435 Italian patients and was externally validated on a cohort of 196 patients (Table 4) (The Cancer of the Liver Italian Program (CLIP) investigators, 1998, 2000). Although the CLIP score has more discriminatory and predictive prognostic power and has been widely used, it has also been noted for some limitations. First, CLIP staging divides patients into six categories based on different variables, but it does not effectively distinguish between subgroups 4–6. Second, the tumor morphology criteria are too general to apply to countries such as Japan where early detection of small liver cancers is quite common. Tumors with a CLIP score of “0” were defined as a single nodular type with a tumor range of less than 50% in the liver. However, since this size is already considered large for a tumor, the prognostic prediction accuracy in the optimal prognostic group (score “0”) is insufficient. Third, the vast majority of patients are classified as CLIP 1 and CLIP 2, and therefore, this staging system has poor stratification capability (Kudo et al., 2003).

2.5 Chinese University Prognostic Index (CUPI) staging system

Due to regional differences in the natural disease history, etiology, and treatment of HCC, the prognostic staging systems developed in Western countries are not fully applicable to Asian populations. Therefore, different countries and organizations in Asia have developed their own staging systems that are applicable to Asian populations. The CUPI system was introduced in 2002 and was developed by analyzing the clinical characteristics of 926 patients with predominantly hepatitis B virus (HBV)-related HCC. The CUPI system considers six independent prognostic factors, namely,

Table 4 Some prognostic staging systems*

Score	ITA.LI.CA	Okuda[1]	CLIP	CUPI[2]	JIS
−4				Asymptomatic disease on presentation	
−3				TNM I and II	
−1				TNM IIIa and IIIb	
0	ITA.LI.CA 0; Child-Pugh score 5; ECOG PS 0; Serum AFP ⩽1000 ng/mL	Tumor size <50% of the liver; Albumin >3 g/dL; No ascites; Bilirubin <3 mg/dL	Unino dular and extension ⩽50%; Child-Pugh grade A; AFP <400 ng/dL; No portal vein thrombosis	TNM IVa and IVb; Total bilirubin <34 μmol/L	Child-Pugh grade A; Japanese TNM stage I
1	ITA.LI.CA A; Child-Pugh score 6 and 7; ECOG PS 1 and 2	Tumor size >50% of the liver; Albumin <3 g/dL; Ascites; Bilirubin >3 mg/dL	Multinodular and extension ⩽50%; Child-Pugh grade B; AFP ⩾400 ng/dL; Portal vein thrombosis		Child-Pugh grade B; Japanese TNM stage II
2	ITA.LI.CA B1; Child-Pugh score 8 and 9; Serum AFP >1000 ng/mL		Massive or extension >50%; Child-Pugh grade C	AFP ⩾500 ng/mL	Child-Pugh grade C; Japanese TNM stage III
3	ITA.LI.CA B2; Child-Pugh score 10–15; ECOG PS 3 and 4			Total bilirubin 34–51 μmol/L; Ascites; Alkaline phosphatase ⩾200 IU/L	Japanese TNM stage IV
4	ITA.LI.CA B3			Total bilirubin ⩾52 μmol/L	
5	ITA.LI.CA C				

ITA.LI.CA: Italian Liver Cancer; CLIP: Cancer of the Liver Italian Program; CUPI: Chinese University Prognostic Index; JIS: Japanese Integrated Staging; TNM: Tumor-Node-Metastasis; ECOG: Eastern Cooperative Oncology Group; AFP: α fetoprotein; PS: performance status. [1] Stage I: 0; Stage II: 1 and 2; Stage III: 3 and 4. [2] Low-risk group (A): score⩽1; intermediate-risk group (B): score=2–7; high-risk group (C): score⩾8. * Data sources: Okuda et al., 1984; The Cancer of the Liver Italian Program (CLIP) investigators, 1998; Leung et al., 2002; Kudo et al., 2003; Farinati et al., 2016.

Table 5 Italian Liver Cancer (ITA.LI.CA) tumor stage*

ITA.LI.CA tumour stage	Tumour	Vascular invasion or metastases
0	Single nodule ⩽2 cm	No
A	Single nodule ⩽5 cm	No
	2 and 3 nodules with a maximum diameter ⩽3 cm	No
B1	Single nodule >5 cm	No
	2 and 3 nodules with a maximum diameter ⩽5 cm	No
B2	2 and 3 nodules with a maximum diameter >5 cm	No
	>3 nodules with a maximum diameter ⩽5 cm	No
B3	>3 nodules with a maximum diameter >5 cm	No
	Any nodules	Yes (intrahepatic)
C	Any nodules	Yes (extrahepatic)

* Data source: Parikh and Singal, 2016.

TNM stage, total bilirubin (TB), AFP, ascites, alkaline phosphatase (ALP), and absence of clinical symptoms, classifying patients into three risk groups (low, intermediate, and high) (Table 4) (Leung et al., 2002). The CUPI study group performed prospective validation on a cohort of 595 HCC patients with predominantly chronic HBV infection. The results showed that CUPI and CLIP staging systems had the best performance in terms of discriminatory power, homogeneity, and gradient monotonicity, with superior overall performance compared to BCLC staging system (Chan et al., 2011). To verify whether CUPI is also applicable to Western populations, the researchers recruited 1048 patients with HCC from the UK (567) and Hong

Kong of China (517). The CUPI system was found to be the most appropriate staging system for patients with HCC receiving palliative care in both the UK and Hong Kong (China) cohorts, as compared to BCLC and CLIP. However, the prognostic performance of CUPI was found unsatisfactory for patients receiving radical treatment (Chan et al., 2014).

2.6 HKLC staging system

Based on a retrospective analysis of 3856 patients with HCC in Hong Kong, a research team from the University of Hong Kong developed the HKLC staging system in 2014. This system is similar to the BCLC staging system in that the former also incorporates ECOG PST, CPS, tumor status, and extrahepatic vascular metastases, but better stratifies patients with intermediate and advanced BCLC into different subgroups, and suggests a more aggressive approach to treatment, resulting in a greater survival benefit for patients (Tables 6 and 7) (Yau et al., 2014). Several studies from China, Singapore, and Korea, which are regions with a high prevalence of HBV-related HCC, also supported that HKLC staging is better than BCLC staging in the prognosis prediction of patients with HCC in Asia. However, the HKLC staging system is not applicable to Western populations (Yan et al., 2015; Selby et al., 2017; Lee et al., 2018). Adhoute et al. (2015) validated BCLC staging and HKLC staging on a cohort of 665 patients with HCC from France; they found no difference between HKLC staging and BCLC staging in patient survival prediction, and HKLC staging did not have a better predictive value of outcome than BCLC staging. This may be attributed to differences in the etiology and treatment modalities, as in European countries, most patients do not have access to more aggressive treatments. Another study on a cohort of 1693 patients with HCC from Spain, the UK, and Switzerland reported that the BCLC staging system was better at predicting OS than the HKLC staging system (Kolly et al., 2016). Therefore, HKLC staging remains to be further validated for Western populations.

2.7 Other staging systems in the Asian region

The JIS score is a prognostic staging system proposed by the Liver Cancer Study Group of Japan (LCSGJ) in 2003 by retrospectively analyzing the clinical data of 722 patients with HCC. The JIS score incorporates the CPS and TNM staging systems based on LCSGJ criteria, which is superior to CLIP staging in terms of selecting the best prognostic group and stratification ability (Tables 4 and 8) (Kudo et al.,

Table 6 Hong Kong Liver Cancer (HKLC) tumor classification*

Tumor	Diameter (cm)	Nodule number	Intrahepatic venous invasion
Early	≤5	≤3	No
Intermediate	≤5	>3	No
	≤5	≤3	Yes
	>5	≤3	No
Locally-advanced	≤5	>3	Yes
	>5	>3	Any
	Diffuse tumor		

* Data source: Yau et al., 2014.

Table 7 Hong Kong Liver Cancer (HKLC) staging system*

Stage	Tumor	ECOG, Child	EVM	Treatment
I	Early	ECOG 0, Child A	No	Resection/liver transplantation/ablation
IIa	Early	ECOG 1/Child B	No	Resection/liver transplantation/ablation
IIb	Intermediate	ECOG 0/1, Child A	No	Resection
IIIa	Intermediate	ECOG 0/1, Child B	No	Transarterial chemoembolization
IIIb	Locally-advanced	ECOG 0/1, Child A/B	No	Transarterial chemoembolization
IVa	Any tumor	ECOG 0/1, Child A	Yes	Systemic therapy
IVb	Any tumor	ECOG 0/1, Child B	Yes	Systemic therapy/supportive care
Va	Early	ECOG 2–4/Child C	No	Liver transplantation
Vb	Early	ECOG 2–4/Child C	Yes	Supportive care
	No early tumor	ECOG 2–4/Child C	Any	Supportive care

ECOG: Eastern Cooperative Oncology Group; EVM: extrahepatic vascular invasion/metastasis. * Data source: Yau et al., 2014.

2003). Since the liver function is relatively better in patients with HCC undergoing hepatectomy, Nanashima et al. (2004) proposed a modified liver injury grade provided by LCSGJ instead of Child-Pugh grade, for a better prognostic classification of liver function (using indocyanine green 15-min retention rate (ICGR15) instead of encephalopathy). Their study showed that the modified JIS scoring system yielded significant differences in disease-free survival (DFS) and OS in each score, outperforming the Japanese TNM staging system. Similar results were obtained in another prognostic study of 230 patients from Japan after liver resection for HCC: the modified JIS score showed the best ability to predict OS based on disease staging and better prognosis compared to the JIS score, CLIP staging, and modified CLIP staging (Nanashima et al., 2006). In addition, because ascites and hepatic encephalopathy are highly subjective among the five indicators of Child-Pugh staging, the use of the ALBI score has been proposed to replace the Child-Pugh staging in the JIS score (i.e., the ALBI-based JIS (ALBI-T) score). The results suggested that the ALBI-T score has better prognostic performance than the JIS score and can prevent clinicians from providing overtreatment (Chan et al., 2016). Although the JIS score and its modified JIS score have shown their applicability to HBV (China)- and hepatitis C virus (HCV) (Japan)-associated HCC, they have been rarely evaluated in Western countries, and hence their applicability to patients with HCC in Western countries needs further research.

China is the world's leading country for liver cancer indicence, accounting for more than half of all new and dying HCC patients. Due to the large number of patients with HCC, the high mortality rate, and differences in the etiology from Western countries, it is crucial to establish a suitable staging system for Chinese patients. The China Liver Cancer (CNLC) staging system, proposed within the scope of 2019 Chinese guidelines, is based on the patient's general condition, liver tumor condition, and liver function, and consists of six parameters (PS, Child-Pugh, extrahepatic metastasis, vascular invasion, and the number and size of tumors). In this system, patients are divided into four stages (Ia/b, IIa/b, IIIa/b, and IVa) and assigned reasonable treatment options (Table 9) (Zhou et al., 2020). A cohort study of 307 patients with HCC from Shandong, China, also confirmed that CNLC is the most appropriate staging system among the four staging systems (CNLC, TNM, BCLC, and CLIP) to predict survival in China (Su et al., 2016).

Table 8 Japanese Tumor-Node-Metastasis (TNM) stage*

Variable	Score
Tumor	
Single	0
Multiple	1
Size (cm)	
<2	0
≥2	1
Vessel invasion	
No	0
Yes	1

* T1=score 0; T2=score 1; T3=score 2; T4=score 3; N0: no regional lymph node metastasisl; N1: regional lymph node metastasis; M0: no distant metastases; M1: distant metastases; Stage I: T1, N0, M0; Stage II: T2, N0, M0; Stage III: T3, N0, M0; Stage IV: T4, N0, M0/any T, N1, M0/any T, any N, M1. Data source: Kudo et al., 2003.

3 Prognostic models for patients with HCC treated by surgery

Surgery, as one of the most important treatment options for early- to mid-stage HCCs, is highly effective in improving patients' survival time. However, the long-term survival of patients is still threatened by tumor recurrence. In patients undergoing surgical resection, a high 5-year recurrence rate has been recorded, often at an early stage (over 70% occurring within two years) (Marrero et al., 2018). Moreover, while the rate of recurrence after liver transplantation is low (11%–18%), when it does occur, the disease often progresses rapidly, with a median survival time of less than two years (Filgueira, 2019; Verna et al., 2020). Although more than a dozen clinical stages of HCC exist, most of them are not constructed exclusively based on patients who underwent surgery. Moreover, the effectiveness of staging systems in the prognosis prediction of surgery patients needs to be further evaluated (Chan et al., 2018). In addition to the prognostic factors included in the staging systems described above, there are also indicators of prognostic value (such as microvascular infiltration and inflammation-related markers) that were not included, which affect the prognostic accuracy of the model (Xu et al., 2019, 2020). Therefore, several studies have supported the further construction of a postoperative prognostic

Table 9 China clinical staging and treatment pathway for HCC*

Stage	PS	Liver function	Extrahepatic metastases	Blood vessel invasion	Number of tumor	Size of tumor (cm)	Treatment
Ia	0–2	Child A/B	No	No	1	⩽5	Surgical resection/ablation/liver transplantation (UCSF)
Ib	0–2	Child A/B	No	No	1	>5	Surgical resection/TACE/ablation or in combination with TACE/liver transplantation (UCSF)
					2, 3	⩽3	
IIa	0–2	Child A/B	No	No	2, 3	>3	Surgical resection/TACE/combination with ablation/liver transplantation (UCSF)
IIb	0–2	Child A/B	No	No	⩾4	Any	TACE/surgical resection/systematic treatment of Sorafenib, Lenvatinib, or FOLFOX4/second-line: Regorafenib
IIIa	0–2	Child A/B	No	Yes	Any	Any	TACE/systematic treatment of Sorafenib, Lenvatinib, or FOLFOX4/second-line: Regorafenib/surgical resection/radiotherapy
IIIb	0–2	Child A/B	Yes	Any	Any	Any	Systematic treatment of Sarafenib, Lenvatinib, or FOLFOX4/second-line: Regorafenib/TACE/radiotherapy
IV	0–2	Child C	Any	Any	Any	Any	Systematic supportive treatment/palliative treatment and care/liver transplantation (UCSF)
	3, 4	Any					

UCSF: University of California, San Francisco; HCC: hepatocellular carcinoma; PS: performance status; TACE: transcatheter arterial chemoembolization; FOLFOX4: oxaliplatin, 5-fluorouracil, and leucovorin. * Data source: Zhou et al., 2020.

model for HCC in conjunction with clinical features that affect the survival of patients as another viable strategy (Table 10).

3.1 Prognostic model for HCC patients undergoing liver resection

For most patients with early-stage HCC, hepatic resection is the preferred choice of treatment, increasing the patient's DFS time (Forner et al., 2018). Unfortunately, tumors are prone to recurrence and metastasis after hepatectomy, with a tumor recurrence and metastasis rate of 40%–70% within five years, seriously threatening the long-term survival of patients with HCC. Therefore, there is an urgent need to develop a model that can effectively predict the prognosis of HCC patients undergoing hepatic resection, to assist clinicians with survival time (Forner et al., 2018; Zhou et al., 2020).

A nomogram, which is a reliable tool for assessing a patient's prognosis, provides risk assessment based on the characteristics of the patient and the disease, thus guiding appropriate clinical decision-making (Balachandran et al., 2015). Huo et al. (2020) conducted a retrospective analysis of 366 patients with HCC who underwent liver resection. The study endpoint was set as OS time, and six independent prognostic factors were included in the nomogram, such as age, BCLC stage, tumor size, serum albumin, alanine transaminase (ALT), and AFP, which were obtained by Cox multi-factor regression analysis. The accuracy of the nomogram was then assessed using the calibration curve and *C*-index. The calibration curves showed a high degree of agreement between the predicted and actual observed 1-, 3-, and 5-year survival curves for the column line graph, demonstrating the good performance of the nomogram. The *C*-index of the model (one, three, and five years) and the corrected *C*-index (one and three years) after 500 bootstrap resamples were all greater than 0.70. Additional 156 patients from the same medical center were subsequently included to verify the stability of the model, and the results showed that the predicted values of OS in the calibration curve were in good agreement with the actual results. Moreover, the *C*-indexes at one, three, and five years were 0.72, 0.72, and 0.69, respectively, which illustrated the accuracy of the nomogram (Huo et al., 2020).

The defibrillation threshold (DFT) risk score model, which was developed using a retrospective multicenter study in China, could predict relapse-free survival (RFS) in patients with hepatectomized HBV-associated HCC. The researchers included 162 patients as a training group and used Cox univariate and multifactorial analyses to obtain three prognostic factors including fibrosis-4 (FIB-4) score, grade of differentiation, and total tumor volume. Patients were categorized into stages A, B, C, and D based on these index scores, and the accuracy of the model was assessed using ROC curve analysis.

Table 10 Prognostic models for patients with HCC treated with surgery

Type of surgery	Number of patients	Model	Primary endpoint	Variable	Reference
Liver resection	522	Nomogram	OS	Age, BCLC stage, tumor size, serum prealbumin, ALT, and AFP	Huo et al., 2020
	255	DFT risk score	RFS	FIB-4, differentiation grade, and TTV	Qin et al., 2019
	2282	EHBH-MVI score	OS, RFS	AFP, tumor tegument, tumor diameter, HBeAg, HBV DNA load, tumor number, and gastric fundal/esophageal varices	Zhang XP et al., 2019
	3903	ERASL-pre score, ERASL-post score	RFS	ERASL-pre score: sex, ALBI score, AFP, tumor size, and tumor number ERASL-post score: sex, ALBI score, AFP, tumor size, tumor number, and MVI	Chan et al., 2018
	771	Nomogram	OS, DFS	OS: TNM stage, albumin, and ALRI DFS: TNM stage, albumin, ALRI, and tumor size	Liao et al., 2021
	978	Nomogram	PRS	Antiviral treatment, time from primary resection to recurrence, size and site of the recurrent tumor, number of recurrences, AFP level at recurrence, and ALBI grade	He et al., 2018
Liver transplantation	846	Nomogram	Risk of recurrence	Tumor grade/differentiation, vascular invasion, nondownstaged tumors outside Milan criteria, pretransplant NLR, radiographic maximum tumor diameter, maximum AFP, and total cholesterol	Agopian et al., 2015
	339	Pre-MORAL, post-MORAL	RFS	Pre-MORAL: preoperative neutrophil ratio, maximum AFP, and tumor size Post-MORAL: grade 4 tumor, vascular invasion, tumor size, and the number of tumors	Halazun et al., 2017
	1359	Competing-risk regression model	OS	The sum of tumor number and size with lgAFP	Mazzaferro et al., 2018

HCC: hepatocellular carcinoma; OS: overall survival; BCLC: Barcelona Clinic Liver Cancer; ALT: alanine aminotransferase; AFP: α fetoprotein; DFT: defibrillation threshold; RFS: relapse-free survival; FIB-4: fibrosis-4; TTV: total tumor volume; EHBH: Eastern Hepatobiliary Hospital; MVI: microvascular invasion; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ERASL: early recurrence after surgery for liver tumor; ALBI: albumin-bilirubin; DFS: disease-free survival; TNM: Tumor-Node-Metastasis; ALRI: aspartate aminotransferase to lymphocyte ratio index; PRS: post-recurrence survival; NLR: neutrophil to lymphocyte ratio; MORAL: model of recurrence after liver transplantation.

The results showed that the values of the AUC for DFT model 1-, 3-, and 5-year subjects were 0.7317, 0.7031, and 0.6972, respectively, which were significantly higher than those of the HKLC (0.6993, 0.5069, and 0.5072), BCLC (0.6421, 0.5400, and 0.5361), and TNM (0.6775, 0.5183, and 0.5152) staging systems. The predictive value of the model was further validated using an internal validation cohort (n=93) and 83 patients from two other medical centers, and the results were consistent with the training set, with all AUC values of the DFT model outperforming those of the other three staging systems (Qin et al., 2019).

Microvascular invasion (MVI) has been strongly associated with early recurrence and reduced survival in patients who underwent HCC surgery; however, no models exist that predict the prognosis of patients with complete (RO) resection hepatectomy for MVI HCC (Cong et al., 2016). To address this issue, Zhang XP et al. (2019) established the Eastern Hepatobiliary Hospital (EHBH) MVI scoring system. The investigators conducted a retrospective analysis of 1033 MVI HCC cases with RO hepatectomy. Seven parameters, including AFP, tumor encapsulation, tumor diameter, hepatitis B e antigen (HBeAg) positivity, HBV DNA load, tumor number, and gastric fundal/esophageal varices, were obtained by Cox univariate and multifactorial analyses to establish the EHBH-MVI score. A score of 4 was selected as the cut-off value based on ROC analysis, and the patients were categorized into high-risk and low-risk groups. The results showed significant differences in median survival time and survival rates at one, three and five years between the two subgroups, both for OS and RFS. A retrospective cohort (n=924) and an internal prospective cohort (n=322) from three

additional medical centers were included for validation, and the EHBH-MVI score performed well in both OS and RFS prediction. To further demonstrate the prognostic performance of the EHBH-MVI score, the AUC values of the EHBH-MVI score were compared with those of the existing commonly used clinical staging systems (BCLC, TNM 7th edition, Okuda, and CLIP) using the EHBH-MVI score. The EHBH-MVI score had the best predictive power for OS and RFS at one, three, and five years in the training cohort. Notably, since most patients have an HBV infection background, the score may not be applicable to areas with different HCC etiologies (Zhang XP et al., 2019).

In a similar study, to develop pre- and post-operative models for assessing the 2-year risk of recurrence, Chan et al. (2018) included 3903 patients with HCC undergoing radical surgical resection. First, the pre- and post-operative clinical characteristics of 387 patients (HBV predominant) from Hong Kong were subjected to univariate and multivariate analyses. The following preoperative independent prognostic factors were identified: male gender, ALBI score, AFP, tumor size, and tumor number. Then, additional MVI factors were obtained as independent post-operative prognostic factors. Subsequently, pre-operative (early recurrence after surgery for liver tumor (ERASL)-pre score) and post-operative (ERASL-post score) models were developed by weighting the above factors. Patients were then divided into low-, medium-, and high-risk groups using the 50th and 80th percentiles of the score as the cut-off values, respectively. The results for the internal validation cohort (n=130) and external validation cohorts from China (HBV, n=1304), Japan (HCV, n=615), USA (mixed etiology, n=661), and Italy (HCV, n=742) also showed that the two models were effective in classifying patients into three subgroups with significantly different RFS time. In addition, comparison by statistical methods revealed that the ERASL-pre score and ERASL-post score models had the best predictive power in both the training cohort and the internal validation cohort, outperforming the TNM staging, Singapore liver cancer recurrence score, and the Korean model. Overall, these two models are applicable not only in areas where HBV and HCV are endemic, but also in areas of mixed etiology, thus showing wider applicability than other models.

Another study of 771 HCC patients undergoing radical resection revealed that the aspartate aminotransferase to lymphocyte ratio index (ALRI) is an independent prognostic factor for HCC patients, and a new postoperative ALRI model was constructed for prognosis prediction (Liao et al., 2021). The researchers first compared the predictive performance of ALRI, systemic immune-inflammation index (SII), and neutrophil to lymphocyte ratio (NLR) based on ROC curve analysis. They found that ALRI had the highest prognostic value, and determined its best cut-off value as 22.6 (Halazun et al., 2009; Wang et al., 2020; Liao et al., 2021). Subsequently, Cox analysis was performed in the training cohort (n=416) to identify the independent prognostic factors of OS in HCC patients: TNM stage, albumin, and ALRI. Moreover, additional tumor size factors were obtained as independent DFS prognostic factors. The above factors were included in the nomogram to predict OS and DFS in HCC patients after one, three, and five years. The verification results showed that the C-indexes of the OS and DFS of the training cohort were 0.705 and 0.678, respectively, and those of the validation cohort (n=355) were 0.711 and 0.666, respectively. In addition, the AUC values of OS and DFS at one, three, and five years in both training and validation cohorts were greater than 0.7.

A nomogram is mainly used to predict the RFS and OS of patients, but less often applied to predict post-recurrence survival (PRS). Unlike patients who have not relapsed, the prognosis of patients with relapsed HCC is related not only to tumor characteristics, but also to the treatment modality received after relapse (Tabrizian et al., 2015). Therefore, the aforementioned nomogram model does not accurately prognosticate the survival of relapsed patients, thus warranting the development of a prognostic model suitable for patients with relapsed HCC. He et al. (2018) included 638 patients who underwent recurrence after hepatectomy as a training set, and parameters such as antiviral treatment, time from primary resection to recurrence, size and site of the recurrent tumor, number of recurrences, AFP level at recurrence, and ALBI grade were obtained as independent prognostic factors by univariate and multifactorial analyses. The above parameters were incorporated into the nomogram, which was used to predict the 2- and 5-year PRS rates. The validation results showed that the C-index of the nomogram (0.797) was significantly higher than that of the BCLC staging (0.713) in the training set. In addition, the model predictions in the calibration curve were highly consistent with the actual values. Similarly, the C-index of the model was significantly higher for the

internal validation set (n=213; 0.756) and the external validation set (n=127; 0.747) than that in the BCLC staging system (0.671 and 0.643).

3.2 Prognostic model for patients with HCC receiving liver transplantation

Liver transplantation, a major treatment strategy for patients with early-stage HCC, has been associated with the risk of tumor recurrence. Once tumor recurrence and metastasis occur, the disease progresses rapidly with an extremely poor prognosis. Although several criteria for liver transplantation have been proposed both nationally and internationally to maximize patient benefit, there is still controversy about which criteria should be used for liver transplantation (Filgueira, 2019). Therefore, many studies have attempted to develop models that can accurately predict the prognosis of patients with liver transplantation HCC and can be used to guide the frequency of post-transplant monitoring and adjuvant therapy (Moris et al., 2020).

Agopian et al. (2015) constructed the first nomogram for predicting recurrence in patients after liver transplantation. A total of 865 patients who received liver transplantation were included in the study, and seven independent prognostic factors, including tumor grade/differentiation, vascular invasion, nondownstaged tumors outside the Milan criteria, pretransplant NLR, radiographic maximum tumor diameter, maximum AFP, and total cholesterol, were identified through multivariate analysis. The risk score was subsequently calculated by weighting the above parameters to predict the patient's risk of recurrence at one, three, and five years. Further investigation showed that the nomogram (C-statistic 0.85) had a better ability to differentiate patients with recurrence than the AJCC T-staging system (C-statistic 0.80).

Halazun et al. (2017) included 339 patients who underwent liver transplantation in a prospective study, with the primary study endpoint being RFS. The following preoperative characteristics were obtained as independent prognostic factors by Cox regression analysis: preoperative NLR >5, AFP >200 ng/mL, and tumor size >3 cm. The preoperative model of recurrence after liver transplantation (pre-MORAL) was developed accordingly, and patients were categorized into low-, medium-, high-, and very high-risk groups, with significant differences in RFS among the groups. In addition, the investigators developed a post-operative model (post-MORAL) using patients' post-operative pathological features with the following variables: grade 4 tumor, vascular invasion, tumor size >3 cm, and number of tumors >3. Similarly, post-MORAL categorizes patients into low-, medium-, high-, and very high-risk groups, with significantly different prognoses among the groups. The pre-MORAL (C-statistic 0.82) model and the post-MORAL (C-statistic 0.88) model featured significantly better differentiation ability than the Milan criterion (C-statistic 0.63) and the University of California, San Francisco (UCSF) criterion (C-statistic 0.57); however, their clinical applications have not been reported.

The prognosis of liver transplantation HCC is closely related not only to HCC-related factors (tumor recurrence) but also to non-HCC-related factors such as chronic rejection and the prevalence of other cancers (Noordzij et al., 2013). Therefore, a more reliable prediction of the prognosis of liver transplantation HCC can only be made if the risk of death from different causes is differentiated. To assess the factors associated with tumor-specific mortality and the risk of death in patients with liver transplantation HCC in competing risk settings, Mazzaferro et al. (2018) performed a competing risk model analysis with multiple endpoint events. A total of 1359 patients with liver transplantation HCC were included in their retrospective analysis, with 1018 patients from Italy as the training cohort and 341 patients from Shanghai as external validation cohort. The results of regression analysis showed that the sum of the tumor number and size with lgAFP was an independent factor for HCC-specific mortality. A prognostic model was then constructed using the above variables to predict 5-year HCC-specific survival rate. The mean C-statistic for the training cohort was 0.780, indicating the good prognostic accuracy of the model. For the validation cohort, the model continued to outperform the Milan, UCSF, Up-to-7, Shanghai-Fudan Standard, and French models in terms of discriminatory power.

4 Conclusions

In summary, the highly heterogeneous nature of patients with HCC has hampered the development of a universally accepted surgical staging system. The most widely used clinical staging system is currently the BCLC staging system. As most of these prognostic

models have been extensively validated, they have good stability and are commonly used for the prognostic assessment of HCC. However, each of these models has their particular limitations. First, as most of the staging parameters are still somewhat controversial, a multicenter large sample validation of these parameters or refinement based on the highest level of evidence is necessary. Second, some staging parameters are not comprehensive enough to be included as indicators of prognostic value. Furthermore, there are limitations for the applicability of the above prognostic models to certain populations, and the best prognostic model often differs between regions with various backgrounds of development, stages of liver cancer, and treatment modalities. In contrast, new models constructed by assessing all clinical characteristics of surgically treated patients with HCC (including the commonly used staging) and validated in different medical centers, are more reliable and accurate in predicting the prognosis of patients with HCC. In fact, new models (e.g., Nomogram, ERASL score, and EHBH-MVI score) have superior prognostic performance compared with common staging systems. Unfortunately, such models have received little attention from other researchers, and few studies have been conducted to further validate their stabilities. Moreover, there have been few reports of subsequent clinical applications. Therefore, these models should be subjected to extensive prospective validation through clinical trials, which may better guide HCC treatment.

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Author contributions

Ziqin HE and Jiazhou YE drafted and revised the manuscript. Xiaomin SHE, Ziyu LIU, Xing GAO, and Lu LU were responsible for the topics, final editing, and preparation of the manuscript for submission. Julu HUANG, Cheng LU, Yan LIN, and Rong LIANG critically revised the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Ziqin HE, Xiaomin SHE, Ziyu LIU, Xing GAO, Lu LU, Julu HUANG, Cheng LU, Yan LIN, Rong LIANG, and Jiazhou YE declare that they have no conflict of interest.

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