Chapter

Prognostic Factors Associated with Postoperative Outcomes After Resection of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

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Abstract

The Barcelona Clinic Liver Cancer (BCLC) staging system is one of the best-known models used for treatment allocation and prognostic evaluation of patients with hepatocellular carcinoma (HCC). However, there is an increasing body of evidence that other clinical, laboratory, pathologic, and molecular features, alone or combined with different scoring systems, can reliably identify subgroups of patients with either poor prognosis after liver resection (LR) or better prognosis than those of the patients included in the same American Joint Committee on Cancer (AJCC) or BCLC stage. For example, among patients with HCC at BCLC stage B, several scores were able to identify subgroups with a similar prognosis to BCLC stage A, suggesting that these patients should be candidates for hepatectomy rather than transarterial chemoembolization (TACE). On the contrary, at present, there are available nomograms and on-line calculators that combine clinical and pathologic characteristics to better identify patients with an increased risk of very early recurrence after LR for intrahepatic cholangiocarcinoma (ICC); such patients should undergo alternative therapeutic approaches to improve their survival outcomes and avoid futile operations. Furthermore, some scores that incorporate clinical and laboratory data have outperformed TNM/BCLC staging in predicting prognosis after resection of ICC or HCC. In recent years, machine-learning, classification, and regression tree models have been used to generate homogeneous groups of patients with distinct outcomes. Such models are useful not only for risk stratification but also for guiding treatment allocation. A detailed analysis of this evidence is presented in this chapter.

Keywords: hepatocellular carcinoma, intrahepatic cholangiocarcinoma, prognosis, liver resection, survival, recurrence

1. Introduction

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most frequent primary malignancies of the liver. In the first six editions of the American Joint Committee on Cancer (AJCC) staging system, these tumors were staged according to the same clinico-pathologic criteria. A better understanding of the pathogenesis of primary liver cancers, as well as the larger volume of data (accumulated in the last decade of the twentieth century and during the first decade of the current century) regarding the distinct prognosis of these tumors, led to the introduction of different staging systems for HCC and ICC in the seventh edition of the AJCC staging system released in 2010 [1]. Because treatment allocation is mainly based on pathologic staging, this was a turning point in the therapeutic approach to these patients. However, refinements in the prognostic evaluation of these patients have been achieved later, leading to updates in the ICC staging system in the eighth edition of the AJCC manual [2]. Moreover, because evidence-based prognostic information emerges very quickly, since 2021, the AJCC staging manual has moved from editions to versions to keep pace with the increasing amount of data.

Distinct risk factors associated with postoperative outcomes of patients with HCC and ICC are presented below.

2. Methodology

This is a review chapter aiming to highlight recent updates related to the prognosis of patients with resected HCC and ICC. To find the most recent literature regarding this issue, a literature search was performed on this topic. To identify the recent literature on the topic of HCC, a search of the PubMed database was conducted using the following terms: (((hepatocellular carcinoma[Title/Abstract]) AND (resection[Title/Abstract])) AND (prognostic factor[Title/Abstract])) AND (english[Language]). The filter "in the last 5 years" was then applied.

For the identification of the most recent papers on the topic of ICC, a PubMed search was performed using the following syntax: (((intrahepatic cholangiocarcinoma [Title/Abstract]) AND (resection[Title/Abstract])) AND (prognostic factor[Title/Abstract])) AND (english[Language]). The filter "in the last 5 years" was further applied.

The abstracts have been evaluated, and the relevant papers were extracted. The full version of each relevant paper has been read. The relevant references from these papers have been evaluated to identify additional articles that were not found during the initial search.

3. Results

The PubMed searches, according to the above-mentioned criteria, generated 166 results for HCC and 59 results for ICC. After evaluating these results, 131 papers from these searches have been used. Additionally, the results of another 136 references retrieved from these papers have been presented. Because of the heterogeneity of the studies, the results were presented and discussed as a narrative review chapter.

4. Discussion

4.1 Hepatocellular carcinoma

In 1999, the Barcelona group introduced a staging system for prognosis and treatment allocation in patients with HCC [3], called the Barcelona Clinic Liver Cancer (BCLC) Staging Classification. This prognostic system evaluates not only the malignant tumor but also the underlying liver disease and the patient's general condition, assessing both clinical and paraclinical (radiologic and laboratory) findings, such as performance status, Child-Pugh score, number and diameter of tumors, vascular invasion, and extrahepatic spread of HCC. Because more prognostic information with direct impact on therapeutic approaches has emerged during the last decade, in 2022, the updated version of the BCLC strategy for prognosis prediction and treatment recommendation was launched [4].

Although the updated versions of the BCLC staging system extended the indications for a curative approach in patients with HCC, according to the current indications of the BCLC system, only a minority of patients could undergo a potentially curative therapy. For this reason, experienced centers in liver surgery explored the potential benefit of liver resection (LR) in patients with advanced-stage HCC (BCLC stage B/C). Thus, a few prognostic factors associated with a favorable long-term outcome after hepatectomy for BCLC stage B/C HCC emerged.

4.1.1 Prognostic factors to select patients for LR beyond standard recommendations

In patients with preserved liver function and multinodular disease (BCLC stage B) or portal invasion (BCLC stage C), LR is not recommended according to the current Western guidelines [4–6]. However, many East-Asian centers have a much more liberal policy regarding LR for patients with advanced HCC. Thus, the Japanese, Chinese, and Korean guidelines for the management of HCC [7–9], as well as the Asian Pacific Association for the Study of the Liver consensus recommendations on HCC [10], suggest that LR offers a significant survival benefit (compared to non-surgical approaches) in selected patients with large and/or multinodular (more than three nodules) HCC and preserved liver function. The validity of this recommendation was confirmed by a randomized controlled trial (RCT) performed in China, which randomized 173 patients with multinodular HCCs beyond Milan criteria to either LR or transarterial chemoembolization (TACE). The overall survival (OS) rates at one, two and three years after LR (76.1%, 63.5%, and 51.5%, respectively) were significantly higher than those achieved by TACE (51.8%, 34.8%, and 18.1%, respectively) [11]. Furthermore, a meta-analysis of 18 high-quality studies, which included almost 6,000 patients, confirmed that hepatectomy was associated with significantly higher OS rates compared to TACE in patients with BCLC stage B/C HCC [12].

The Hong Kong group developed a staging system in 2014, which included treatment recommendations to allocate different therapeutic approaches [13]. The Hong Kong Liver Cancer (HKLC) staging system adopted a more liberal approach to LR, which is also recommended for patients exceeding BCLC stage A. While the BCLC system is usually used in Western centers, the HKLC staging system was widely accepted in Asian centers [14]. In selected subgroups of patients, treatment recommendations according to the HKLC system were associated with significantly better long-term outcomes compared to the therapeutic options suggested by the

BCLC system in similar patients. For example, in those patients with BCLC stage B HCC who fulfilled the criteria for inclusion in HKLC stage II, the five-year OS achieved by curative therapies was significantly higher compared to TACE (52.1% vs. 18.7%; $p < 0.001$). Even in BCLC stage C patients classified as HKLC stage II, radical approaches have been associated with significantly improved five-year OS rates compared to the results of systemic therapies (48.6% vs. 0%; $p < 0.0001$) [13].

Supported by such results reported in Asian series [11, 15–18] and meta-analyses of these series [19, 20], high-volume institutions from Western countries started to perform LR in selected patients with advanced-stage HCC [21, 22].

A meta-analysis published by Stevens et al. [20] in 2017 revealed that LR was associated with better survival outcomes in patients with solitary HCC larger than 5 cm compared to the results achieved by TACE in similar patients. Then, a multicentric study published in 2019 divided the BCLC A patients into two subgroups: those with a single tumor larger than 5 cm (BCLC A1 group) and the other patients fulfilling BCLC criteria for inclusion in stage A (solitary nodule 2–5 cm or two to three nodules smaller than 3 cm; BCLC A group) [23]. Among the 814 patients included, 8.4% were classified as BCLC 0, 38.1% as BCLC A, 34.3% as BCLC A1, and 19.3% as BCLC B. Five-year OS rates after curative-intent hepatectomy across BCLC 0, A, A1, and B stages were 86.2%, 69%, 56.9%, and 49.9%, respectively. Although the OS rates achieved in BCLC A1 patients were significantly lower than those of BCLC 0/A patients ($p = 0.0016$), there was no statistically significant difference in OS between BCLC A1 and BCLC B patients ($p = 0.259$). These findings suggest that patients with BCLC B disease who undergo LR have similar long-term outcomes to those with large solitary HCC (> 5 cm) who should undergo LR according to BCLC recommendations, supporting the consideration of resection even in selected BCLC B patients if the tumors are safely resectable. This data suggests that BCLC B should not represent an absolute contraindication to surgery and that refinement of the BCLC algorithm is needed to more accurately reflect the heterogeneity of resectable HCC.

Indeed, the long-term results achieved by hepatectomy in patients with BCLC 0/A HCC were significantly superior to those achieved in patients with BCLC B/C HCC, but even in the latter group, the long-term oncologic outcomes seem to justify hepatectomy in carefully selected patients. Thus, five-year OS rates ranged between 60%–65% in BCLC stage 0/A patients and 50%–57% in BCLC stage B, while five-year DFS rates in BCLC 0/A or B stages ranged between 35%–45% and 20%–29%, respectively [24, 25].

For example, in a multi-institutional retrospective study involving 1,434 patients operated on in high-volume Western centers, after a median follow-up of 37 months, the incidence of recurrence was 28.8% in BCLC 0 patients, 49.2% in BCLC A, and 64.2% in BCLC B. Also, three-year RFS differed significantly by BCLC stage: 73.7% versus 50.6% versus 24.4% ($p < 0.001$) in BCLC 0, BCLC A, and BCLC B [26]. Regarding the dynamics of recurrence, BCLC 0 patients had a later peak (at 7.2 months) compared to BCLC A patients, who had the earliest peak (at 2.4 months). Distinct from these two groups, BCLC B patients had two peaks at 4.2 months and at 22.8 months. These distinct types of recurrence intervals might recommend a more tailored postoperative follow-up regimen according to the BCLC stage, as well as the tumor burden and alpha-fetoprotein (AFP) level [26]. However, although recurrence after curative-intent resection of HCC increased progressively with advancing BCLC stage, the lack of recurrence at three years in one out of four patients with BCLC stage B seems to justify hepatectomy even in such patients.

Another retrospective analysis of a multi-institutional cohort, published in 2020 by Tsilimigras et al. [27], evaluated recurrence behavior and long-term outcomes in patients receiving hepatic resection either within BCLC treatment recommendations (BCLC 0/A) or beyond them (BCLC B/C). Patients with BCLC B/C disease had a higher frequency of multifocal recurrence and a significantly higher rate of early recurrence, especially within the first two postoperative years. The one-year recurrence rate was 38.3% in the BCLC B/C group compared with 21.3% in the BCLC 0/A group. DFS rates at one, three and five years were 75.1%, 46.1%, and 27.3% for BCLC 0/A versus 56.9%, 27.1%, and 22.2% for BCLC B/C (p <0.001). OS at one, three and five years was 90.7%, 85.6%, and 76.9% for BCLC 0/A versus 82.4%, 64.4%, and 51.6% for BCLC B/C (p = 0.003). In patients beyond BCLC criteria for LR, AFP >400 ng/mL and R1 resection were independent predictors of recurrence [27]. Although patients undergoing hepatectomy beyond BCLC indications (BCLC B/C) have worse oncologic outcomes and earlier recurrence compared to those within recommended criteria, survival remains acceptable in carefully selected BCLC B/C cases. Moreover, a multicentric study on 1,010 patients assessed the probability of cure after resection of HCC, according to the BCLC stage, by using a non-mixture cure model with DFS as the primary endpoint [28]. In the entire cohort, the probability of being cured after HCC resection was 42.2%, with a median time to cure of 3.35 years. For BCLC 0/A stage patients, the probability of cure was 47.6%, and the time to cure was 3.56 years. Even in patients who are not candidates for LR according to the BCLC staging system (BCLC-B), the probability of being cured was 37.6% after 3.12 years. Notably, for BCLC-B patients, preoperative AFP was the only independent predictor of cure. The highest probability of cure (46.7%) was observed in patients with AFP <10 ng/mL, while those with AFP ranging between 10 and 400 ng/mL had a 21.9% chance of cure, and the lowest probability of cure was observed when preoperative AFP exceeded 400 ng/mL (7.1%; p = 0.017).

These findings emphasize that surgical resection may still provide curative benefits beyond current treatment allocation guidelines, supporting a more nuanced application of the BCLC system.

Although the BCLC staging system is the most widely used classification for treatment allocation, few studies have tried to refine the prognosis of the patients included in the different BCLC stages and further identify discrete subgroups with similar prognoses.

Such data have contributed to the development of therapeutic indications within the updated versions of the BCLC, explaining the emergence of new versions after the initial edition was published in 1999 [3, 4, 29].

To select the patients with advanced HCC who truly benefit from LR, many studies have tried to identify the independent prognostic factors associated with improved survival outcomes.

Most papers dealing with this subject found that the number and largest diameter of nodules were able to stratify patients. Probably the most frequently used method to stratify the prognosis of patients with BCLC stage B HCC is the "up–to-7 criteria" [22, 30]. This system is easy to use and practical because it is calculated as the sum of the number of nodules and the maximum diameter of the largest nodule. Furthermore, Bolondi et al. [22], as well as Kudo et al. [30], recommend the association between the up–to-7 criteria and the Child-Pugh score to stratify BCLC stage B patients. LR or transplantation is recommended mainly for patients with

a Child-Pugh score ranging from 5 to 7 points and fulfilling the up–to-seven criteria. Similar criteria were proposed by Wada et al. [31], who found that 32 patients with up to three lesions and at least one of them larger than 5 cm, or four nodules irrespective of their diameter, had better one-, three-, and five-year OS (84%, 74%, and 63%, respectively) compared to 19 patients with five or more liver nodules (64.9%, 55.7%, and 37.1%, respectively).

A multicentric study that evaluated 164 patients who underwent curative-intent LR for multinodular HCC exceeding the Milan Criteria found that the only factors independently associated with poor OS were high tumor burden score (TBS) and preoperative AFP levels higher than 400 IU/mL [32]. In HCC (similar to colorectal liver metastases [33]), TBS is a surrogate parameter aimed at evaluating the volume of HCC and is calculated using the formula: TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2 [34]. According to the TBS value, the patients were divided into three groups: low TBS (<5.83), medium TBS (5.83–11.18) and high TBS (≥ 11.18). The TBS was able to stratify patients with multinodular HCC beyond Milan criteria in discrete subgroups with significantly different OS outcomes (low TBS vs. medium TBS vs. high TBS – five-year OS: 70.2% vs. 54.7% vs. 16.7%, respectively; p <0.001) [32]. Furthermore, the authors developed a TBS-based preoperative score, calculated according to the formula: TBS-based pre-score = 0.117 × TBS + 0.085 × (cirrhosis yes: 1, no: 0) +0.227 × (ASA >II: 1, ASA ≤II: 0) + 0.642 × (AFP >400: 1, AFP <400: 0). According to this score, the patients were divided in three risk groups, as follows: low risk (≤0.88), intermediate risk (0.88–2.03) and high risk (>2.03). This TBS-based preoperative risk score was also able to stratify patients in terms of OS (low risk vs. intermediate risk vs. high risk – five-year OS: 66.3% vs. 25.2% vs. NR, respectively; p = 0.012) and cumulative incidence of early recurrence (less than two years) – low risk versus medium risk versus high risk: 48.5% versus 67.3% versus 73.5% (p = 0.029) [32]. Additional independent predictors included, among BCLC-B patients, ASA grade higher than II and poor/undifferentiated histology [34].

Considering all these data, a risk score based on clinical characteristics (number of nodules, largest diameter, ASA score, liver cirrhosis), pathologic features (lymphovascular invasion, poor or undifferentiated tumor grade), and AFP level was able to preoperatively identify the patients with multinodular HCC who have the highest benefit after LR [32].

Similarly, a nomogram based on three parameters (AFP–TBS – ATS score, BCLC stage, and AST to ALT ratio – AAR) had high predictive power to forecast early cancer-related death (less than one year) due to recurrence of HCC in patients with BCLC stage B/C. This nomogram should guide surgeons to avoid futile hepatectomies in such patients [35].

Also, to avoid futile hepatectomies in BCLC stage B/C HCC, the latest version of the EASL clinical guidelines for HCC management recommends the use of bridging or downstaging therapies to allow a positive test of time before considering surgical resection in multifocal HCC involving multiple segments [5].

More recently, due to developments in molecular biology, new biomarkers have emerged. For example, the number of glypican-3 (GPC3)-positive circulating tumor cells (CTCs) has been identified as a prognostic factor for survival after resection of BCLC stage B HCC. While in BCLC stage 0/A HCC the number of GPC3-positive CTCs was not associated with survival outcomes, after resection of BCLC stage B HCC, a high number of GPC3-positive CTCs was significantly associated with

poorer OS and RFS rates compared to patients with low GPC3-positive CTCs ($p = 0.02$ and $p = 0.03$, respectively) [36].

Similar to the previous article, which found distinct prognostic factors for BCLC stage 0/A or B patients, another study used a machine learning Classification and Regression Tree (CART) model to identify the strongest predictors of OS according to the BCLC stage in patients with HCC who underwent hepatectomy [24]. In the preoperative model, AFP and the Charlson Comorbidity Index (CCI) were the most impactful predictors of survival for BCLC stage 0/A patients. For BCLC stage B patients, the TBS was the dominant prognostic factor. In the postoperative model, lymphovascular invasion became the most important predictor of survival for BCLC-0/A patients, followed by preoperative AFP, ASA score, and CCI. For BCLC-B patients, TBS continued to be the primary determinant of long-term prognosis [24]. These findings highlight the potential of TBS-based stratification to expand surgical candidacy beyond traditional BCLC guidelines and personalize postoperative management, while preoperative assessment of AFP and comorbidities, as well as pathologic data regarding lymphovascular invasion, are tremendously important for risk stratification in BCLC stage 0/A patients.

Beyond the above-mentioned factors that may help identify the potential candidates for LR among the BCLC stage B/C patients, a lot of clinical, pathological, genomic, molecular, and laboratory data with direct impact on treatment allocation, intensity of surveillance programs, and patient counseling have not yet been included in the current prognostic systems. For this reason, we present below a structured approach to the prognostic factors associated with survival outcomes after surgical resection of HCC.

4.1.2 Prognostic factors associated with outcomes after LR

4.1.2.1 Short-term outcomes

Since HCC develops in most cases on a cirrhotic liver, the risk of postoperative complications and mortality has always been a concern for surgeons. Because more than 80% of patients develop HCC in the context of chronic liver disease and more than 50% have HCC on liver cirrhosis, the risk of postoperative complications (especially ascites and post-hepatectomy liver failure – PHLF) is higher after resection of HCC compared to hepatectomies performed for other diseases. A constant objective of surgeons dealing with such patients has been to identify methods that would accurately estimate postoperative risks.

For many years, the decision to perform LR in patients with HCC on cirrhosis depended on the **Child-Pugh score**. However, quantification of two out of five parameters included in this score (encephalopathy and ascites) is operator-dependent, and the distinction between grades A and B Child-Pugh could be misleading. Thus, inadequate inclusion of a patient in Child-Pugh grade A (7 points) instead of Child-Pugh grade B (8 points) may be associated with a significant increase in the rate of postoperative complications and, mainly, PHLF. A study by Wang et al. [37] revealed that PHLF rates were 12.2% in grade A Child-Pugh patients, compared to 39.6% ($p < 0.05$) in grade B Child-Pugh patients. To avoid such potential confounding evaluations, more accurate methods were introduced to stratify the risk of postoperative complications and death. For example, the European Association for the Study of Liver Disease (EASLD) recommended evaluating the risk of post-hepatectomy

complications in patients with HCC by considering the following parameters: the presence/absence of portal hypertension, the MELD score, and the anticipated extent of LR [5]. Thus, in patients without portal hypertension, with a MELD score as high as 9, and requiring a minor hepatectomy, the associated risk of postoperative liver decompensation was 5%, and the rate of postoperative death was up to 0.5%. On the contrary, patients with portal hypertension and needing a major LR could experience a risk of liver decompensation higher than 30% and a liver-related mortality of 25% [5].

In patients with cirrhosis, Asian authors usually make the decision to perform or not perform a LR, and determine its extent, according to the indocyanine green retention rate at 15 minutes (ICGR15). Thus, in patients without uncontrollable ascites and with normal bilirubin levels, the decision on the extent of hepatectomy is based on the ICGR15 rate. For ICGR15 rates lower than 10%, major hepatectomies can be safely performed. When ICGR15 rate ranges between 10% and 19%, the resection should be limited to a bisegmentectomy, while a segmentectomy is recommended when ICGR15 is higher than 20% and lower than 29%. Limited resections (less than one segment) are recommended when ICGR15 ranges between 30% and 39%, while ICGR15 ≥40% precludes any LR [38]. Following this protocol, Makuuchi and colleagues reported only one patient death among 685 LRs for HCC [38].

The importance of accurate preoperative evaluation of surgical risks is even higher in elderly or frail patients. Thus, the article "Evaluation of the ACS NSQIP Surgical Risk Calculator in Elderly Patients Undergoing Hepatectomy for Hepatocellular Carcinoma" assessed the effectiveness of the surgical risk calculator (SRC) of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) in predicting morbidity and mortality among elderly patients undergoing curative-intent hepatectomy for HCC. The study included 500 patients aged over 70 years who underwent hepatectomy for HCC between 1998 and 2017. To evaluate the performance of the ACS NSQIP SRC, the study compared 12 postoperative outcomes with the mean predicted risk calculated by SRC. The following parameters were analyzed: major complications, any complication, pneumonia, cardiac complication, surgical site infection, urinary tract infection, venous thromboembolism, renal failure, 30-day readmission, reoperation, 30-day mortality, and discharge to a care facility or palliative care. The majority (324 patients, 64.8%) underwent minor hepatectomies, while 35.2% underwent major hepatectomies. The most common complication was surgical site infection (7.5%), followed by renal failure (4.4%). The rates of pulmonary thromboembolism (PTE; 3.2%) and renal failure (4.4%) exceeded the predicted mean risks (PTE 1.8%; renal failure 1.0%). Conversely, the 30-day readmission rate (7.0%) was lower than the predicted risk (9.4%). The rate of discharge to a care or palliative facility was also lower than estimated (2.5% vs. 5.7%). The model correctly identified only 57.8% of the patients who were readmitted and only 71.2% with respect to mortality [39]. As such, the ACS NSQIP SRC demonstrated limited accuracy in elderly patients undergoing hepatectomy for HCC. Overall, the calculator tended to underestimate the risk of complications such as thromboembolism and renal failure. Because SRC has low accuracy in predicting mortality and discharge to a care facility, a substantial number of cases were misclassified relative to these outcomes. These findings indicate reduced clinical applicability of this tool for risk stratification in elderly candidates for hepatic resection for HCC, highlighting the need for improved predictive models.

Therefore, a parameter that takes into account the values of albumin and bilirubin (called ALBI grade) has been assessed as a prognostic tool for the evaluation of postoperative complications' risk. Thus, the patients with ALBI grade 1 had a significantly lower risk of PHLF and death compared to those with ALBI grade 2 or 3 [40]. This model outperformed the Child-Pugh score and MELD score in terms of the ability to predict posthepatectomy liver failure after HCC resection [37, 40]. Furthermore, ALBI grade was also a prognostic factor associated with long-term outcomes after HCC resection [40].

Many retrospective studies have suggested that laparoscopic LR (LLR) of HCC is associated with significantly improved short-term outcomes [41–45]. Thus, the length of hospital stay [41] and blood loss were significantly lower in patients who underwent LLR compared to open surgery [46, 47]. Furthermore, the rate of postoperative complications (especially the volume of ascites) was significantly lower after LLR compared to the open approach [41, 46, 47]. A propensity score matching analysis evaluated both short-term and long-term outcomes after LR for HCC using either a minimally invasive approach or an open approach [48]. Two 1:1 propensity score–matched groups were compared to ensure similar clinical characteristics. After matching, 407 patients were included in the minimally invasive group and 407 in the open-surgery group. The minimally invasive group achieved significantly lower rates of overall complications, severe complications (Clavien-Dindo ≥III), and 90-day mortality. Hospital stay was notably shorter in patients who underwent the minimally invasive approach (five days vs. eight days in the open group). Furthermore, in a subgroup of 178 patients with portal hypertension, minimally invasive surgery (MIS) continued to demonstrate reduced morbidity and shorter hospitalization compared to open surgery [48]. Similar results have been reported by other case-matched studies with propensity score matching [49, 50]. Even in elderly patients (more than 70 years old) who underwent LR for solitary HCC, the laparoscopic approach has been associated with significantly better short-term outcomes compared to open surgery [50], especially lower rates of pulmonary complications and shorter hospital stay [51]. Indeed, compared to younger patients operated on by the laparoscopic approach, elderly patients who underwent laparoscopic hepatectomies for HCC had increased blood loss and need for blood transfusion, as well as longer operation time and postoperative hospitalization [51]. However, morbidity and mortality rates seem to be similar between young and elderly patients [52–57] with resected HCC, although two studies suggested that postoperative complications and even mortality were higher in the elderly [58, 59]. Overall, it seems that patients older than 70 benefit from MIS at least as much as younger subjects [60, 61].

A meta-analysis published in 2022 by Kabir et al. [62] included 11 studies (one RCT and 10 retrospective studies with propensity score matching) and evaluated the impact of a minimally invasive approach on OS (as the primary end-point) in patients with HCC on liver cirrhosis. Regarding its secondary end-points, the meta-analysis confirmed that the laparoscopic approach was associated with a significant reduction in the rates of both overall and major complications, while the length of hospital stay significantly decreased in the laparoscopic resection group (with a median of 3.22 days) [62]. Although most of these studies included patients who underwent minor LRs, the results of the ORANGEII Plus multicenter RCT suggested that even in patients who underwent major hepatectomies, the laparoscopic approach was associated with a shorter time to functional recovery compared to open surgery, as well as similar rates of major complications and R0 resections [63].

However, a multicentric study with propensity score matching, which compared the results achieved by LR for HCC with textbook outcomes (TO), revealed that the laparoscopic approach favored TO achievement compared to open surgery in patients who underwent minor hepatectomies, but not in those receiving major LRs [64].

Since most elderly patients undergoing LR for HCC also suffer from other debilitating conditions, such as liver cirrhosis, their physiologic reserve is obviously reduced, leading to a decreased ability to recover from surgical stress. That condition, called frailty [65, 66] has a significant impact on short-term results, being associated with higher rates of postoperative morbidity and mortality [67–69], as well as with loss of independence after hepatectomy [70, 71].

4.1.2.2 Long-term outcomes

4.1.2.2.1 Surgical factors

Postoperative complications have been associated with poorer long-term outcomes in most studies [42], although the results were not quite uniform. A monocentric retrospective study from Hong Kong revealed that postoperative complications were associated with significantly lower rates of OS [72], while a multicentric retrospective study including 734 patients operated on in Western centers found that postoperative complications were an independent risk factor for recurrence-free survival (RFS), but not for OS (in multivariate analysis) [73]. Furthermore, the latter study found that only infectious complications were independently associated with lower rates of both OS and RFS, compared to patients who did not develop complications [73]. Similar results have also been reported in Asian series, revealing that either intra-abdominal infections [74, 75] or any type of postoperative infections [76] were significantly associated with inferior long-term outcomes. Because Eastern centers included higher rates of cirrhotic patients compared to Western centers, it seems that the detrimental effect of infectious complications on oncologic outcomes is independent of the presence of liver cirrhosis.

Interestingly, the impact of postoperative complications seems to be more significant in patients who underwent hepatectomy for HCC with more favorable features. A composite score, including the values of AFP and TBS, called alpha-feto protein – tumor burden score (ATS), is calculated according to the formula: $ATS^2 = (\ln AFP)^2 + (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$ [77]. It was revealed that in patients with low ATS, the frequencies of microvascular and major vascular invasion, poor tumor differentiation, and liver capsule infiltration were significantly lower than those observed in patients with high ATS [78]. For this reason, ATS has been proposed as a surrogate parameter for the evaluation of tumor biology (aggressiveness). A retrospective study including 1,124 subjects revealed that in the low/medium ATS group, two-year RFS rates were significantly higher in patients who experienced no or mild complications compared to those who developed moderate or severe complications. On the contrary, patients with high ATS had similar two-year RFS rates irrespective of the degree of postoperative complications (no/mild vs. moderate/severe complications) [79].

LLR was associated with non-inferior [42, 45, 49, 64, 80, 81] or even better survival outcomes compared to the open approach [50, 82, 83]. Even patients with

BCLC stage 0/A HCC and high-risk pathologic features (such as microvascular invasion, poor tumor differentiation, and/or satellite nodules) who underwent laparoscopic hepatectomy had better textbook outcomes compared to the open approach and similar survival outcomes [84]. In high-risk patients, the propensity score matching analysis found that five-year OS and RFS rates were similar between the laparoscopic group (55.6% and 39.6%, respectively) and the open surgery group (55.5% and 36.4%, respectively) [84]. Moreover, a meta-analysis found that LLR significantly reduced the risk of postoperative death (by 16%–26%) compared to the open approach [62]. For these reasons, most guidelines recommend, at this moment, performing minimally invasive LR whenever possible [5–7].

Anatomic LR has been proposed by Makuuchi et al. [85] as the preferred surgical technique in patients with resectable HCC because it enables complete resection of the tumor and micrometastases. This is explained by the frequent dissemination of HCC through the portal system, with almost two-thirds of patients having tumor emboli in the portal vein or its branches [86]. Thus, resection of the entire tumor-bearing portal territory decreases the risk of residual disease and recurrence [87, 88]. Although a few studies did not find a significant survival benefit associated with the type of hepatectomy [89, 90], many reports, coming mainly from Asian countries, revealed a significant correlation between the type of hepatectomy and long-term results [91–94]. Therefore, complete resection of HCC along with the entire morpho-functional unit of the liver containing the tumor might achieve similar RFS rates irrespective of the surgical margin width after anatomical LRs.

Furthermore, a study published by Tsilimigras et al. [95] in 2020 evaluated the impact of surgical margins on the long-term outcomes of patients with T1 HCC who underwent R0 hepatectomies. Margin width (≤1 cm vs. >1 cm) significantly influenced RFS, with one-, three-, and five-year RFS rates of 77%, 48.9%, and 35.3% for patients with narrow margins, versus 81.7%, 65.8%, and 60.7% for those with wide margins. According to the type of hepatectomy, margin width did not significantly influence RFS after anatomical resection, but among patients undergoing non-anatomical resection, a margin larger than 1 cm resulted in significantly better three-year RFS compared with a margin narrower than 1 cm (86.7% vs. 47.3%). These data suggest that anatomical hepatectomies should be the standard approach in patients with resectable HCC, and whenever non-anatomical resections are performed, a surgical margin larger than 1 cm is warranted.

Regarding the relationship between the long-term outcomes and surgical margin width stratified by ATS score, it was observed that in patients with low ATS, wider margins have not been correlated with superior survival outcomes. On the contrary, larger margin width has been associated with significantly higher RFS and OS rates in the high ATS group [78].

Lymph node (LN) dissection is still debatable, since strong evidence supporting its routine use is lacking. The estimated incidence of LN metastases (LNMs) in HCC patients ranges between 4% and 11% [96, 97]. It is well known that in patients with resected HCC, the presence of LNM is associated with poorer prognosis compared to those without LNM [98]. The prognosis of resected patients with LNM was similar to those having HCC and vascular invasion but significantly poorer than that of patients without vascular invasion [98]. Thus, knowledge of LN status allows for better prognostic stratification. However, the indications and clinical impact of LND are not well-established. For example, a survey based on data retrieved from the Surveillance, Epidemiology, and End Results (SEER) database

revealed that 14.3% of patients resected for HCC underwent regional LND (between 2004 and 2013) [99]. Out of 538 patients receiving LND, only 45 (8.4%) were node-positive. Although in univariate analysis LND was associated with higher OS and disease-specific survival (DSS) rates, in multivariate analysis LND was not found to be an independent prognostic factor associated with OS or DSS [99]. Another retrospective analysis evaluated patients with resected HCC who were included in the National Cancer Data Base (NCDB) between 2004 and 2015. Among 8,095 patients, 1,442 (17.8%) underwent hepatectomy and LND, while the remaining 82.2% had LR without LND [100]. In patients with LND, the only independent predictor of pathologic N1 (pN1) was clinical N1 (cN1). Although clinical nodal status had moderate sensitivity (55.1%), its high specificity (98.0%) in predicting pN1 status justifies LND in patients with HCC and cN1 [100]. However, LND has not been associated with higher OS or DFS rates according to an RCT [101] and a meta-analysis [102]. Nevertheless, in LND patients, pN1 status has been associated with significantly lower OS rates compared to pN0 [100, 102]. Thus, LND seems to be useful, especially in patients with clinically positive LNs who undergo resection of HCC, only for purposes of prognostic estimation and adequate tailoring of postoperative follow-up. For these reasons, some authors recommend only LN sampling when clinical suspicion of positive nodes has been raised by preoperative imaging or intraoperative findings [100, 103].

4.1.2.2.2 Clinic and radiologic factors

Among the clinical parameters, the time from diagnosis to LR was evaluated as a potential prognostic factor for survival after LR. Thus, the impact of the interval between diagnosis and surgery (time-to-surgery – TTS) on outcomes of patients with resectable HCC was analyzed in a multi-institutional study published in 2021 by Tsilimigras et al. [25]. The primary endpoints evaluated were OS, disease-free survival (DFS), 90-day mortality, 90-day readmission, and the incidence of postoperative complications. Among 775 patients who underwent LR for HCC, 537 (69.3%) had early surgery (TTS <90 days), while 238 (30.7%) had delayed surgery (TTS ≥90 days). Baseline clinico-pathologic characteristics were similar between the two groups, apart from a higher proportion of major hepatectomies in the early surgery group. For the entire cohort, the median OS was 97.9 months, and the five-year OS rate was 63.9%. The median DFS was 35.4 months, and the five-year DFS rate was 35.5%. The five-year OS (63.7% vs. 64.9%; $p = 0.79$) and DFS (33.5% vs. 42.4%; $p = 0.20$) were similar between the early and late operation groups, respectively. Even after stratification by BCLC stage (0 or A), no significant differences in OS or DFS were observed between the two groups. Furthermore, the delayed-surgery cohort achieved similar 90-day mortality (3.4% vs. 2.1%), 90-day readmission (6.1% vs. 4.6%), and overall complication rates (36.7% vs. 33.2%) compared to the early-surgery group. Moreover, major morbidity (Clavien-Dindo grade ≥III) was more frequent in the early-surgery group (12.8% vs. 6.7%). Although almost one-third of patients with resectable HCC experienced a prolonged waiting period before surgery, a delay of ≥90 days does not appear to negatively impact either short-term or long-term outcomes. Such findings can support improved preoperative optimization and help reduce patient anxiety regarding surgical delays.

Another study published by Hasjim et al. [104] assessed the impact of a six-month wait policy on the outcomes of patients with early HCC (T2N0M0) who

underwent liver transplantation, resection, or ablation. Like the previous study, the survival outcomes were not significantly different between the patients who underwent early or delayed treatment, irrespective of the type of therapy (hepatectomy, transplantation, or ablative treatment).

Clinically significant portal hypertension, a well-known risk factor for the development of postoperative complications and liver decompensation [105, 106], has not been associated with poorer short-term outcomes compared to patients without portal hypertension in the subgroup with Child-Pugh grade A [106] liver cirrhosis. Regarding its impact on long-term outcomes, the five-year OS was significantly lower in patients with clinically significant portal hypertension compared to those without portal hypertension [106–108]. However, in the subgroup of patients with resected HCC and Child-Pugh grade A liver cirrhosis, the results were contradictory, with some series reporting that the presence of clinically significant portal hypertension was not associated with significantly lower OS rates [106], while others found a lower OS rate in the portal hypertension group [107]. After matching patients with and without portal hypertension, Cucchetti et al. [108] did not find a significant difference in OS rates between the two matched groups. A retrospective monocentric study by Kavano found that portal hypertension with esophageal varices was associated with lower OS rates in univariate analysis, but multivariate analysis did not identify this condition as an independent prognostic factor associated with poorer OS [109]. On the contrary, Choi et al. [110] identified clinically significant portal hypertension as the strongest independent prognostic factor for decreased OS. A recent analysis found that clinically significant portal hypertension was not associated with RFS but was an independent prognostic factor for poorer OS after resection of very early or intermediate-stage HCC. In patients with early-stage resected HCC, portal hypertension did not correlate with OS [111]. However, as long as palliative therapies are associated with significantly lower oncologic outcomes, LR should be considered even in patients with clinically significant portal hypertension.

The presence of comorbidities frequently has a negative impact not only on immediate postoperative results but also on long-term outcomes. As has already been mentioned, the Charlson comorbidity index is an independent predictor of OS in patients undergoing LR for BCLC stage 0/A HCC [24].

Furthermore, co-morbid conditions and older age are frequently associated with frailty. Although the impact of frailty on survival outcomes has already been demonstrated in other malignancies, currently, few studies have investigated its impact on long-term outcomes after HCC resection. Yamada et al. [112] found that frailty was significantly associated with poorer OS, DFS, and cancer-specific survival (CSS) rates in univariate analysis, while multivariate analysis revealed that frailty was independently associated only with CSS in patients older than 75 undergoing hepatectomy for HCC. On the contrary, Okada et al. [113] found that frailty was an independent prognostic factor of poor OS in independently living elderly patients (≥ 65 years old) with resected HCC, but was not significantly associated with DFS or CSS.

As it was already mentioned, TBS is useful for prognostic discrimination and selection for resection among patients with advanced-stage HCCs. However, the impact of this clinical score on prognostic stratification of all patients resected for HCC, irrespective of BCLC stage, was also assessed. A large multicentric study, which included 1994 patients, analyzed the ability of TBS to predict the incidence,

timing, and anatomical distribution of recurrence following curative LR [114]. The overall five-year recurrence rate was 50.4%, with recurrence risk increasing with tumor burden, as follows: low TBS – 36.0%, intermediate TBS – 54.4%, and high TBS – 62.5% ($p < 0.001$). Although intrahepatic recurrence was most common across all groups, high-TBS patients more often developed extrahepatic recurrence: 14.3%, 25.9%, and 43.5% in low TBS, intermediate TBS, and high TBS groups, respectively ($p < 0.001$). High-TBS patients were also more likely to experience early recurrence (≤24 months), multiple intrahepatic lesions, and larger recurrent nodules. Moreover, the recurrence hazard peaked earlier and higher in patients with high TBS compared with those with low TBS [114]. Thus, TBS was found to be a strong independent prognostic factor for recurrence after curative-intent HCC resection. Because liver transplantation is a well-established treatment option for recurrent HCC after initial curative-intent hepatectomy, the impact of initial clinical factors on the probability of transplantation at the time of recurrence has been investigated in a multicenter study published by Zhang et al. [115]. The authors also aimed to develop and validate a preoperative risk model predicting non-transplantable recurrence (NTR) to improve initial treatment allocation. Milan and UCSF criteria were used to define transplant eligibility at baseline and recurrence. Among initially transplant-eligible patients who underwent LR, 293 fulfilled the Milan criteria, and 320 fulfilled the UCSF criteria. Of these, 113 (38.6%) and 131 (40.9%) developed recurrence, respectively. NTR occurred in 32 patients (28.3%) based on Milan criteria and in 35 patients (26.7%) based on UCSF criteria. The three preoperative factors that were consistently associated with an increased risk of NTR were the presence of cirrhosis, HCC larger than 3 cm, and tumor multifocality. A risk score was developed by assigning one point for each factor. The patients without any risk factors were included in the low-risk group, those having only one risk factor in the intermediate-risk group, and the high-risk group included the patients having two or three factors. The incidence of NTR increased progressively from low-risk to high-risk groups. Taking into account the Milan criteria, the NTR rates were 4.5%, 13.3%, and 20.5% in low-, intermediate-, and high-risk groups, respectively. Considering UCSF criteria, for low-, intermediate-, and high-risk groups, the rates of NTR were 4.5%, 12.4%, and 33.9%, respectively [115]. Thus, patients with two or three risk factors may derive greater benefit from upfront liver transplantation, whereas hepatic resection remains an appropriate strategy for those with low-risk factors at baseline.

Therefore, high TBS, which is a surrogate marker for large tumors and multinodularity, correlates with aggressive tumor biology, including early, NTR, extrahepatic spread, and multifocal relapse. These findings support individualized postoperative surveillance, whose intensity should be based on tumor burden, with closer follow-up for high-risk patients.

Also, OS declined as TBS increased, with five-year OS of 77.9%, 61.0%, and 39.0% for low, intermediate, and high TBS, respectively ($p < 0.001$) [34]. Notably, there were no meaningful differences in OS between patients with the same TBS across BCLC stages (for example, BCLC-A/intermediate TBS vs. BCLC-B/intermediate TBS showed similar OS). Even more, patients with BCLC-B and intermediate TBS had significantly better five-year OS than those with BCLC-A and high TBS (58.9% vs. 45.0%; $p = 0.005$). On multivariable analysis, TBS remained independently associated with OS in both BCLC stage A and BCLC stage B. For BCLC stage A, intermediate TBS and high TBS carried adjusted hazard ratios of death of 2.07 and

4.05, respectively, versus low TBS. In BCLC stage B, high TBS carried an adjusted hazard ratio of about 3.85 versus low TBS. These results were confirmed in an external validation cohort, with five-year OS of 79.0%, 51.2%, and 28.0% for low, intermediate, and high TBS. TBS was also associated with five-year DFS (40.7%, 35.4%, and 28.5% for low, intermediate, and high TBS) [34]. Thus, TBS provides powerful, stage-agnostic prognostic stratification after HCC resection and can outperform raw BCLC stage in discriminating outcomes. Incorporating TBS can identify BCLC-B patients with prognosis comparable to or better than high-burden BCLC-A disease, supporting more individualized surgical decisions and follow-up intensity.

The follow-up strategy should be tailored according to the risk of recurrence over time, because the recurrence risk and the probability of survival after HCC resection are not constant over follow-up, being dynamic parameters rather than fixed ones. A useful metric for the evaluation of the dynamic changes in survival probability is conditional survival (CS). CS reflects the probability of a patient surviving an additional period of time after having already survived a defined interval. Elfadaly et al. [116] evaluated the impact of TBS and other clinico-pathologic risk factors on CS among 1,040 patients undergoing curative-intent resection of HCC. CS improved over time for all groups. Thus, CS at three years showed persistent differences by tumor burden but demonstrated that high-risk patients who remain recurrence-free for several years move into a more favorable prognostic category over time. For example, patients with high TBS who survived the first three postoperative years experienced a significant increase in their probability of long-term survival, approaching that of patients with intermediate tumor burden. Similarly, the effect of other adverse prognostic factors (poorly differentiated tumor grade, microvascular invasion, liver capsule involvement, and positive margins) on prognosis decreased over time [116]. Consequently, CS provides relevant prognostic information and facilitates personalization of follow-up, decreasing the intensity of monitoring over time even in patients with poor prognostic factors.

Beyond the number and diameter of HCC nodules, a CT scan can evaluate skeletal muscle mass and provide information about sarcopenia. Although sarcopenia was not significantly associated with DFS, it has been proven to be an independent risk factor associated with OS after resection of HCC [117]. Thus, preoperative management of sarcopenia may improve the long-term outcomes of patients with resected HCC.

Macrovascular invasion has long been considered an absolute contraindication to LR and transplantation [118, 119]. However, during the last decade, it has become more of a poor prognostic factor than a formal contraindication for LR [120], as many studies have revealed that even in the presence of intrahepatic vascular invasion, the OS and DFS rates achieved by curative-intent hepatectomy are higher than those achieved by palliative therapy [121–123]. A nationwide survey conducted in Japan demonstrated that LR in patients with portal vein invasion enables a median OS of 2.45 years, which is significantly higher than the 1.1 years observed in non-resected patients ($p < 0.001$) [124]. The authors found that the survival benefit was not dependent on age, etiology of cirrhosis, tumor marker levels, or tumor number. The only subgroup that did not achieve a survival benefit from LR was patients with portal vein thrombosis of the main trunk [124].

4.1.2.2.3 Pathologic factors

Tumor necrosis was also associated with poorer OS and RFS, as well as an increased risk of extrahepatic recurrence. Extensive tumor necrosis (>50%) was an independent predictor of poor long-term survival, and some authors suggested that it should be considered for inclusion in the T-stage stratification of the AJCC staging system for HCC [125].

Microscopic portal vein invasion (MPVI) is one of the most important predictors of poorer survival outcomes in patients with HCC [126, 127]. This prognostic factor is independent of tumor number and size, and it significantly worsens oncologic results regardless of Milan or up-to-7 criteria status [128]. However, the presence of MPVI is difficult to assess before LR. For this reason, few studies have tried to evaluate the predictors of MPVI. The independent predictors of MPVI are age less than 65 years, preoperative diameter of HCC greater than 5 cm, and PIVKAII level higher than 200 mAU/mL [129]. A combined score based on these parameters has proven to be a reliable predictor of microvascular invasion (and survival) in patients resected for HCC [129]. Another modality to preoperatively assess the presence of MPVI is the detection of CTCs in peripheral blood, as MPVI has been significantly associated with the presence of CTCs [130, 131]. A recent study evaluated the presence of CTCs in peripheral blood, portal vein, and hepatic veins of patients who underwent anatomical resections for HCC [132]. The authors found that CTCs were significantly more frequently present in the portal vein (45.8%) than in the hepatic vein (33.5%; $p = 0.031$), but the frequency of CTCs was similar between portal vein samples and peripheral blood (36.9%; $p = 0.122$) [132]. Furthermore, a positive CTC test (either in peripheral blood or portal vein) has been significantly associated with poorer OS and DFS rates [132].

Although the impact of microscopic lymphovascular invasion has been evaluated only in a few series, most of them have suggested that this factor is independently associated with a higher risk of recurrence [93, 114] and poor survival outcomes [133]. Furthermore, lymphovascular invasion has been identified as an independent predictor (hazard ratio [HR] = 2.00; 95% confidence interval [CI]: 1.14–3.50) of recurrence beyond Milan criteria following curative resection of HCC [134].

Poor tumor differentiation has long been considered a significant factor correlated with poor survival outcomes in patients with resected HCC [110, 114]. However, a few studies did not find a correlation between tumor differentiation and survival outcomes [135, 136]. This might be because the impact of tumor differentiation on long-term results achieved by LR for HCC seems to be dependent on tumor size [137]. Shinkawa et al. [138] evaluated the impact of poor differentiation on different long-term outcomes. The authors found poor tumor differentiation to be an independent adverse prognostic factor for OS, early RFS, and early extrahepatic RFS, but not for RFS. Furthermore, poor differentiation was an independent prognostic factor for OS and early RFS only in patients with HCCs larger than 2 cm. Even in patients with HCCs larger than 2 cm (or 5 cm), RFS has not been significantly influenced by poor differentiation [138].

4.1.2.2.4 Laboratory findings

As was previously mentioned, the AFP level is a strong prognostic factor associated with oncologic outcomes in patients resected for HCC [139].

AFP level adds biological insight to tumor morphology and should be used together with TBS to guide clinical decision-making and postoperative surveillance intensity. The potential synergism between AFP level and TBS has been evaluated in a multi-institutional retrospective study, including almost 900 patients [140]. Both AFP and TBS were strong independent predictors of survival, but these two prognostic factors have a combined prognostic effect. Thus, patients with low/intermediate TBS and high AFP had significantly worse outcomes compared with those with low/intermediate TBS and low AFP. Similarly, among patients with high TBS, low AFP was associated with better survival than high AFP. Furthermore, the patients with low TBS but high AFP had outcomes similar to those with high TBS but low AFP [140].

A retrospective analysis by Tsilimigras et al. [141] evaluated the prognostic impact of serum AFP levels at the time of recurrence (rAFP) on post-recurrence survival outcomes in patients undergoing curative-intent hepatectomy for HCC. Patients with rAFP >10 ng/mL had significantly worse 3-year OS than those with rAFP ≤10 ng/mL, both in early recurrence (30.1% vs. 60.2%; p <0.001) and late recurrence (18.0% vs. 78.7%; p = 0.03) group. The prognostic significance of rAFP level (≤10 ng/mL vs. >10 ng/mL) was independent of the salvage treatment modality – three-year OS rates: ablation (76% vs. 41.1%, respectively), intra-arterial therapy (46.1% vs. 12.9%, respectively), repeat hepatectomy (100% vs. 37.5%, respectively), and salvage transplantation (100% vs. 60%, respectively) [141]. Multivariable analysis demonstrated that rAFP >10 ng/mL was associated with a two-fold increased risk of death after recurrence. Thus, AFP levels at the time of recurrence serve as a strong and independent prognostic factor. Measuring rAFP can help stratify patients with recurrent HCC and guide expectations and treatment planning following relapse.

Moreover, the correlation of AFP with other prognostic factors was able to ensure a more accurate prognostic stratification of these patients. Hence, a composite parameter called the AFP model turned out to be useful in selecting patients with HCC who significantly benefit from hepatic resection. The AFP model was initially designed for selecting HCC patients for liver transplantation, proving superior to other scores (such as MELD) in predicting transplant benefit [142, 143]. It is calculated by scoring the following parameters: maximum HCC size (≤3 cm – 0 points; 3–6 cm – 1 point; >6 cm – 4 points), number of tumors (≤3 tumors – 0 points; ≥4 tumors – 2 points), and AFP value (≤100 ng/mL – 0 points; 100–1,000 ng/mL – 2 points; >1,000 ng/mL – 3 points) [140]. Among BCLC B/C patients, the subgroup with an AFP score ≤2 had a significantly more favorable five-year OS (54.5% vs. 39.4%, respectively) and lower recurrence risk (45.2% vs. 61.8%, respectively) compared to those with an AFP score ≥3. Conversely, among patients with BCLC 0/A stage, the subgroup with an AFP score ≥3 had a higher five-year recurrence risk (47.9% vs. 38.4%, p = 0.046) and a significantly lower five-year OS rate (47.8% vs. 65.9%, p < 0.001) compared to the subgroup with an AFP score ≤2 [144]. Therefore, the AFP model was able to adequately stratify patients according to their prognosis across all the BCLC stages. Furthermore, it could identify BCLC 0/A HCC patients with unfavorable outcomes after hepatectomy, as well as a subgroup of BCLC B/C patients who might benefit from hepatic resection. Thus, the AFP model should be considered in the selection algorithm for HCC patients eligible for curative hepatic resection, as well as for developing new postoperative surveillance strategies among patients at high risk of recurrence.

Another AFP-based scoring system, called the TAC score, evaluated TBS, AFP level, and Child-Pugh grade [145]. Low, intermediate, or high TBS were scored with 0, 1, or 2 points, respectively; according to the AFP level (≤400 ng/mL or >400 ng/mL), the patients had 0 or 1 point, respectively; Child-Pugh grade A or B allocated 0 or 1 point, respectively. Therefore, the TAC score ranges from 0 to 4 points. Among more than 1,400 patients analyzed, the TAC score effectively stratified survival. Three-year OS decreased progressively with rising TAC scores (88.8%, 81.2%, 68.1%, and 59.6% in TAC 0, TAC 1, TAC 2, and TAC 3/4, respectively), and five-year OS followed the same pattern (81.4%, 66.5%, 51.1%, and 32.3% according to TAC 0, TAC 1, TAC 2, and TAC 3/4 scores, respectively). Furthermore, each 1-point increase in the TAC score was associated with a significant increase in mortality risk. RFS also worsened progressively with higher TAC scores [145]. This simple risk score, based entirely on preoperative parameters that are easy to assess clinically, was useful for the prediction of recurrence and OS following hepatectomy for HCC. Therefore, the TAC score is a strong, easy-to-use prognostic tool that outperforms the BCLC classification and other traditional models. It captures both tumor biology and morphology, as well as underlying liver function, allowing more precise stratification of surgical candidates and more personalized postoperative surveillance.

Beside AFP, another blood marker frequently-used in Asian centers to evaluate the prognosis of patients with HCC is des-gamma-carboxy prothrombin (DCP), also known as "PIVKAII." According to some authors, DCP (higher than 60 mAU/mL) is a more effective tumor marker than AFP in the prognostic estimation of patients undergoing LR for HCC [31, 139]. In patients with multinodular disease, Wada et al. [31] found that PIVKAII ≥400 mAU/mL has been marginally associated with better OS compared to PIVKAII <400 mAU/mL (p = 0.077), while the AFP level did not reach statistical significance (p = 0.188).

Although a few retrospective studies revealed that the ALBI grade [146] can accurately stratify patients with resected HCC according to their prognosis [40, 147], the ALBI grade 2 is a heterogeneous prognostic group because it encompasses patients with a wide range of liver functional reserve. For this reason, Hiraoka et al. [148] used the modified ALBI score to further stratify patients with ALBI grade 2 into two uniform subgroups with distinct survival outcomes [147, 148]. This modified score, which is largely used in Asian countries, is still less frequently used in the Western world. Another modality to stratify patients with ALBI grade 2 into discrete groups with distinct outcomes is based on the evaluation of the albumin level. Thus, patients with albumin levels lower than 3.5 mg/dL had lower OS and PFS rates compared to those with higher albumin levels. Furthermore, the low albumin group was associated with a significantly higher incidence of multiple recurrences compared to the high albumin group (which developed solitary recurrences more frequently) [149]. The correlation of low albumin levels with poor long-term outcomes after curative treatment of HCC, irrespective of ALBI grade, has also been suggested by Sonohara et al. [150]. Consequently, nutritional support and albumin supplementation might be useful to improve survival outcomes after resection of HCC.

However, the ALBI grade does not evaluate portal hypertension, which is frequently encountered in patients with HCC. For this reason, platelet count has been incorporated into a new prognostic score as a surrogate marker for portal hypertension. The new score is called the platelet-bilirubin-albumin (PALBI) grade,

calculated according to the formula: PALBI grade = (2.02 × $\log_{10}$total bilirubin) + (−0.37 × [$\log_{10}$total bilirubin]^2) + (0.04 × albumin) + (−3.48 × $\log_{10}$platelets) + (1.01 × [$\log_{10}$platelets]^2). The patients were divided into three categories according to the PALBI score: grade 1 ≤ −2.53, −2.53 <grade 2 ≤ −2.09 and grade 3 > −2.09 [151]. The discriminatory ability of the PALBI grade was significantly better than those of the Child-Pugh score, MELD score, and ALBI grade, with the area under the curve (AUC) of the PALBI grade having significantly higher values compared to the other methods [151]. Furthermore, unlike the ALBI score, the PALBI grade was able to differentiate each BCLC stage into three groups with significantly different prognoses [152].

Beyond these scores that evaluate mainly the degree of liver dysfunction, the assessment of immunologic status may be useful because immune dysregulation might be associated with tumor recurrence after LR. For example, lymphopenia may reflect an immunologic status associated with cancer-related immune tolerance [153, 154]. A recent retrospective study revealed that both preoperative and surgical stress-induced postoperative lymphopenia (less than 1,000/μL) have been associated with significantly reduced OS and DFS rates [155]. Different from isolated lymphopenia, the composite immunologic scores evaluate the multiple immune pathways involved in cancer proliferation and recurrence, offering more refined tools to predict long-term outcomes after HCC resection. Thus, the inflammation scores evaluate systemic inflammatory response (SIR), which is associated with postoperative survival outcomes in most cancer types [156–158]. In patients undergoing LR for HCC, high systemic immune-inflammation index (SII) [159, 160], increased baseline neutrophil-to-lymphocyte ratio (NLR) [160, 161], decreased lymphocyte-to-monocyte ratio (LMR) [162], and higher aspartate aminotransferase-to-platelet ratio (APRI) [160] have been significantly associated with poor OS and DFS rates. Perioperative dynamic changes of the inflammation indexes reflect the response to surgical stress and ischemia-reperfusion, allowing an indirect evaluation of the immunologic status during the perioperative interval. Two retrospective studies revealed that the increased postoperative values of NLR compared to preoperative levels (ΔNLR) have been significantly associated with recurrence and OS after HCC resection [163, 164].

Resection of HCC developed in patients with hepatitis C viral infection (HCV-HCC) has traditionally been associated with worse long-term outcomes compared to patients with HCC and non-HCV infection. In a retrospective analysis with propensity score matching published by Wei et al. [165] in 2020, it was observed that during the period 2000–2009, HCV-HCC patients showed significantly worse five-year OS compared with non-hepatitis HCC (Non-Hep-HCC) patients (12% vs. 63%, respectively; p = 0.029). However, during the more recent period (2010–2017), survival in the HCV-HCC group significantly improved and even surpassed that of Non-Hep-HCC patients (five-year OS: 86% vs. 73%, respectively; p = 0.035). Among the 196 patients with HCV-HCC, treatment information was available for 137, and 77 (56%) received direct-acting antiviral (DAA) therapy prior to surgery. Patients who received DAA therapy demonstrated significantly better five-year OS than untreated patients (69% vs. 54%, p = 0.016) [165]. These data outline that long-term survival in HCV-HCC patients has improved due to advances in antiviral therapy, while long-term outcomes in Non-Hep-HCC patients have remained unchanged and are currently poorer. These findings highlight important clinical, pathological, and prognostic differences between the two subtypes.

Similar results have been reported recently in the Asian population. Patients with HCV-HCC operated on during the period after the advent of DAA therapies experienced significantly higher RFS rates compared to those achieved by similar patients operated on before the introduction of DAA treatment (2.8 years vs. 2.1 years, respectively) [166]. Furthermore, the achievement of sustained virologic response (either before or after surgery) was associated with significantly higher OS rates compared to patients without sustained virologic response [127, 166, 167].

Furthermore, in the subgroup with a low Japan Integrated Staging Score, the HCV-positive patients had significantly lower DFS and OS rates compared to the HBV-positive group [168].

4.2 Intrahepatic cholangiocarcinoma

Until the seventh edition of the AJCC staging system (implemented in 2010), ICC was not staged independently but rather according to the same criteria as HCC. To assess the prognostic accuracy of this first independent ICC staging system, a multicentric study published in 2011 evaluated a cohort of 449 patients and demonstrated that the AJCC/UICC seventh edition T categories successfully stratified ICC patients into groups with distinct prognoses [169]. Although tumor size was not an independent predictor of OS in that study, other research has shown that increasing tumor size is independently associated with lower OS and correlates with higher rates of microvascular invasion and poor differentiation [170–173]. These data supported the inclusion of tumor size in the eighth edition of the AJCC staging system.

Following the introduction of the eighth edition of the AJCC system in 2016, a comparative analysis between the new and previous ICC staging systems was conducted in a cohort of 1,154 patients [174]. It was found that, in general, more advanced stages (according to the eighth edition) correlated with lower five-year OS. However, patients with stage II disease had better five-year OS than those with stage IB, and those with stage IIIA disease had superior survival compared to stage IB and II. Thus, while the eighth edition improved risk stratification for T3 and stage III patients, it failed to adequately differentiate outcomes among other subgroups. Similar results have been reported by Kang et al. [175].

In this context, a multi-institutional study published in 2021 presented these paradoxical findings and proposed a modified TNM system (mTNM), which showed superior prognostic accuracy [176]. The proposed mTNM staging defines the following prognostic categories:

T categories:

- T1 – Solitary tumor ≤5 cm without vascular invasion
- T2 – Solitary tumor >5 cm without vascular invasion
- T3 – Solitary tumor with vascular invasion
- T4 – Multiple tumors, or periductal-infiltrating type, or direct invasion of extrahepatic structures

N categories:

- N0 – No regional LN metastases
- N1 – 1–2 positive regional LNs
- N2 – ≥3 positive regional LNs

Stage grouping:

- IA – T1N0M0
- IB – T2N0M0
- IIA – T3N0M0
- IIB – T4N0M0, T1–2N1M0
- III – T3–4N1M0, T1–2N2M0
- IV – T3–4N2M0 or any T with M1

The new mTNM classification was associated with a monotonic decrease in survival, both in the multi-institutional cohort (median OS: stage I – 69.8 months, stage II – 37.1 months, stage III – 18.9 months, stage IV – 16.4 months; all $p < 0.05$) and in the SEER dataset (median OS: 87, 29.3, 17.7, and 14.2 months in stage I, II, III, and IV, respectively; all $p < 0.05$) [176]. This prognostic stratification remained valid even among patients with ≥6 LNs examined. In conclusion, through empirical analysis, the T categories were redefined and combined with new nodal classification levels, leading to a revised mTNM staging system. The proposed system better stratified long-term survival compared to the current edition of the AJCC staging system and should be considered for inclusion in future revisions of the AJCC staging.

In the seventh edition, ICC with regional LNM was categorized as stage IVA. In the updated AJCC eighth edition, the finding of N1 was downgraded from IVA to IIIB [177]. An analysis of the SEER database revealed that LN status information was available for only 49% of patients undergoing resection for ICC [178]. Furthermore, there are no established guidelines regarding the minimum number of LNs that should be retrieved and evaluated. In the eighth edition of the AJCC staging for ICC, it is recommended to harvest at least six LNs for complete nodal staging, aligning with the recommendations for gallbladder cancer [2, 179]. Unfortunately, the median LN yield reported, even when LN dissection (LND) is performed, is only three LNs across various studies [180, 181]. Furthermore, an important observation was that fewer than 30% of ICC patients had at least six excised LNs [182]. Among patients without LND (Nx), long-term survival was heterogeneous: Nx patients had survival outcomes similar to N1 patients during the first 18 postoperative months, but those surviving more than 18 months had long-term outcomes comparable to N0 patients [182]. Moreover, while the prognosis of N0 patients was influenced by the number of HLN (<6 vs. ≥6), long-term survival in N1 patients was not [182].

These findings highlight the prognostic importance of lymphadenectomy and the need to remove at least six nodes for adequate staging of resected ICC patients.

However, numerous researchers have recommended performing a routine lymphadenectomy during hepatic resection for ICC due to the significant prognostic implications associated with nodal disease status. In fact, metastasis to the LNs is among the most critical indicators of an unfavorable prognosis [183–187].

In cirrhotic patients, caution is warranted, as lymphadenectomy carries a significantly higher postoperative complication risk (especially infectious) compared with non-cirrhotics [188]. In such cases, the decision for lymphadenectomy could be guided by an improved radiologic model, integrating clinical (age), laboratory (CA 19-9, albumin, bilirubin), and imaging (tumor number, LN appearance) data to predict the probability of nodal metastasis. This model demonstrated excellent predictive performance (c-index >0.70) [189] and was complemented by a user-friendly online calculator, enhancing its clinical applicability. This tool can aid preoperative decision-making and prognostic stratification in patients not undergoing lymphadenectomy [189].

4.2.1 Patient-related factors

Certain patient demographics and comorbid conditions have been associated with prognosis in ICC. Age is an important factor, with advanced age being linked to worse survival, whereas younger patients tend to fare slightly better. Sex differences have been observed inconsistently; some large analyses suggest that male patients have worse survival than female patients, although this has not been universally confirmed [190]. General health status markers, especially nutritional and performance status, are also prognostic. Thus, malnutrition and frailty correlate with inferior survival outcomes. In particular, sarcopenia (loss of skeletal muscle mass) has been linked to worse survival in ICC patients undergoing resection [191].

4.2.2 Clinical and surgical factors

The impact of clinical factors (such as tumor number and size) on survival outcomes in patients with resected ICC, as well as their therapeutic implications, has been examined in several studies.

It was found that patients with large (>5 cm) or multifocal ICC had significantly lower OS and DFS rates compared to those with a single tumor <5 cm, although postoperative morbidity and mortality rates were similar. Among patients with large or multifocal ICC, the subgroups most likely to benefit from hepatectomy could be identified based on the absence of nodal metastases and/or well/moderate differentiation [192]. Furthermore, a meta-analysis published in 2014 by Mavros et al. [193], including 57 studies, concluded that larger tumor size, the presence of multiple tumors, LNM, vascular invasion, and poor tumor differentiation are factors associated with shorter OS. Treatment and prognosis for patients with ICC: systematic review and meta-analysis [193].

Although patients with two resected ICC nodules had a five-year OS of 28% (comparable to those with solitary ICC), resection in patients with three or more tumors should be carefully considered and reserved for selected individuals, possibly those with a favorable response to neoadjuvant chemotherapy [194, 195]. Regarding the benefit of resection versus other available therapies for patients

with multifocal ICC, a study published in 2022 by Franssen et al. [196] compared OS between patients treated with hepatic arterial infusion pump (HAIP) chemotherapy using floxuridine and those treated by hepatic resection. A total of 319 patients with multifocal ICC were included (141 in the HAIP group and 178 in the resection group) [196]. The HAIP group included a higher proportion of patients with bilobar disease (88.0% vs. 34.3%), larger tumors (median 8.4 cm vs. 7.0 cm), and a greater proportion with ≥4 lesions (66.7% vs. 24.2%). The 30-day postprocedural mortality was 0.8% for HAIP versus 6.2% for resection. OS rates were similar between the two groups (median OS of 20.3 months for HAIP and 18.9 months for resection). Five-year OS for patients with two or three lesions was 23.7% (HAIP) versus 25.7% (resection), while for those with ≥4 lesions, it was 5% versus 6.8%, respectively [196]. Given the short- and long-term outcomes observed, multifocal ICC resection must be evaluated cautiously due to the high complication rates after major hepatectomy – since postoperative morbidity and complication severity were independent predictors of reduced RFS and OS [197]. Thus, minor or even major hepatectomy may still be justified in patients with good performance status and only two to three hepatic nodules, whereas HAIP chemotherapy should be viewed as an effective alternative in those with high surgical risk and/or advanced disease (large tumor diameter, ≥4 lesions, nodal metastases). Resection might also be beneficial in patients who respond favorably to HAIP and maintain good performance status. Preoperative intra-arterial chemotherapy may therefore help select patients with favorable tumor biology who can achieve meaningful survival benefits from surgery.

This is particularly relevant since other studies have shown no significant OS benefit from systemic neoadjuvant chemotherapy [198], while adjuvant systemic chemotherapy has shown only modest improvements, mainly in subgroups with advanced tumors [199–201]. Furthermore, the PUMP-2 trial, a nonrandomized multicenter phase II study including 50 patients, showed that combining HAIP chemotherapy with floxuridine and systemic gemcitabine-cisplatin in patients with unresectable liver-confined ICC resulted in one- and three-year OS rates superior to gemcitabine-cisplatin alone [202]. However, Edeline et al. [203] published in 2019 a phase II clinical trial that evaluated the response rate after selective internal radiotherapy (SIRT) plus chemotherapy in patients with unresectable ICC. The findings suggested that combination chemotherapy and SIRT have antitumor efficacy as an initial treatment strategy for inoperable ICC. Moreover, a notable percentage of patients experienced sufficient tumor reduction to become eligible for surgical intervention [203].

The benefit of anatomic versus non-anatomic resection remains controversial. A single-center retrospective study with propensity score matching, including 3,880 patients, revealed that anatomic resection improves the long-term survival of ICC with comparable postoperative complications [204]. Furthermore, a metaanalysis published in 2025 by Jiang et al. [205] suggested that AR, compared to NAR, can improve OS and DFS without increasing perioperative risks, particularly in ICC patients with tumors larger than 5 cm. Another study indicated that the width of the surgical margin is more significant than the type of hepatectomy [206]. Regarding resection margin width, a positive margin (R1) correlated with inferior OS and RFS, and survival decreased progressively when margins were lower than 1 cm [207]. Similarly, a systematic review from China, which included nine studies, reported that patients with ICC who underwent curative hepatectomy with a negative margin

≥10 mm may have a long-term survival advantage [208]. Although a margin <1 cm should not contraindicate resection, surgeons should aim for at least a 1 cm margin to optimize survival outcomes.

MIS, including laparoscopic and robotic approaches, is increasingly used in surgical resection for ICC. While oncologic principles must be respected, some high-volume centers have reported favorable results with MIS for ICC. The findings suggest a potential benefit of MIS in terms of decreased blood loss, fewer intraoperative and postoperative transfusions, shorter length of stay, and reduced perioperative morbidity, with no difference in operating time, Pringle maneuver duration, perioperative mortality, R0 resection rate, rate of lymphadenectomy, DFS, or OS rates [209–211]. Furthermore, Wei et al. [212] compared patients undergoing laparoscopic LR for large (≥5 cm) or multiple (≥2) ICCs with patients who underwent laparoscopic hepatectomy for small solitary ICCs, and also with patients who underwent open surgery for large or multiple ICCs (N = 20). They found that short- and long-term outcomes were similar between all three groups of patients [212]. Furthermore, another study from Italy, published in 2024, found that among patients at risk for very early recurrence (VER), MIS was associated with improved long-term outcomes [213].

Three-year post-recurrence survival was better among patients who underwent repeat hepatectomy versus other treatments (54.0% vs. 13.0%; $p = 0.001$) [214]. However, only 9% of patients were eligible for repeat resection, and even then, median survival was modest (26 months), as most developed a second recurrence within 12 months [214].

4.2.3 Laboratory factors

In addition to clinical predictors, several laboratory markers have demonstrated significant prognostic value for resected ICC patients. Although these factors cannot contraindicate hepatic resection, they allow prognostic stratification, can suggest the use of preoperative oncologic therapy to select surgical candidates, and can guide postoperative surveillance intensity.

The well-established serological biomarker is carbohydrate antigen 19-9 (CA 19-9), a tumor marker often elevated in ICC. High preoperative CA 19-9 levels have been correlated with adverse outcomes. Patients with markedly elevated CA 19-9 are more likely to have LNMs, experience early recurrence after resection, and have worse OS [215, 216]. In one large study, a CA 19-9 cut-off of 38 U/mL was able to stratify patients, with significantly higher survival rates being observed in those with CA 19-9 levels lower than 38 U/mL compared to patients having higher values of CA 19-9 [217]. Even a meta-analysis confirmed that serum CA 19-9 is an independent prognostic factor for postoperative survival [218]. In cases with normal CA 19-9 levels, carcinoembryonic antigen (CEA) could identify high-risk patients. An elevated CEA, though less commonly high in ICC, has been associated with poorer OS and PFS rates compared to patients with normal CEA [219]. Moreover, the combination of CA 19-9 and CEA levels was able to further discriminate prognosis. Moro et al. [220] revealed that five-year OS was significantly higher in patients with low CA19-9 and low CEA (54.5%) compared with those with low CA19-9/high CEA (14.6%), high CA19-9/low CEA (10.0%), and high CA19-9/high CEA (0%; $p < 0.001$).

When combined with other clinical and laboratory data, the prognostic accuracy of CA 19-9 (and CEA) has improved. For instance, among patients with

low CA19-9/low CEA, a high NLR and large tumor size were significantly associated with a one-year survival reduction. In fact, NLR >5 was independently associated with markedly decreased OS (p = 0.002) in all resected ICC patients [221]. Similar results have been reported by Chen et al. [222]. Furthermore, in a retrospective cohort study, the authors reported that preoperative NLR was prognostic of both overall recurrence and early recurrence after curative-intent resection of ICC [223]. Another study from MD Anderson Cancer Center, published in 2017, revealed that the NLR ratio is independently associated with worse survival in patients with up-front resected ICC or after neoadjuvant treatment [224].

Platelet-to-lymphocyte ratio (PLR) has also been studied among patients with resected ICC. A monocentric retrospective study from China, including 322 patients, suggested that preoperative PLR might represent a novel independent prognostic factor for OS and RFS in ICC patients undergoing hepatic resection [225]. Additionally, high PLR was an independent prognostic factor for short PFS and OS in patients with unresectable ICC receiving gemcitabine-cisplatin chemotherapy [226].

Systemic inflammation index (SII), another parameter reflecting immune-inflammatory status, also correlated significantly with OS. While both SII and NLR were independent predictors of OS, only SII independently predicted CSS [227].

The ALBI score was another validated prognostic tool. A multicenter study investigated the impact of ALBI grade on short- as well as long-term outcomes among patients with ICC. The study showed that higher ALBI grades were independently associated with worse OS. Median OS declined progressively with increasing grade (grade 1: 49.6 months, grade 2: 29.6 months, grade 3: 16.9 months; p <0.001) [228]. This association was obvious in both cirrhotic and non-cirrhotic patients. Additionally, ALBI grade 2/3 patients had higher perioperative transfusion needs, prolonged hospital stays (>10 days), and higher 90-day mortality rates [228]. Moreover, a meta-analysis published in 2025 by Omouri-Kharashtomi et al. [229], which included 13 studies with 3,434 patients, found that a high ALBI grade indicates poor OS and RFS in patients with cholangiocarcinoma, especially the intrahepatic type [229].

Also, a composite score based on the level of albumin and lymphocyte count, called the prognostic nutritional index (PNI), is associated with tumor biology and survival. Thus, decreased values of PNI were significantly more frequently observed in patients with multifocal disease and represented an independent predictor of poor survival after controlling for tumor factors [230]. A composite laboratory score based on CA 19-9, platelet count, NLR, and albumin level (called LabScore) was developed to enhance prognostic accuracy. Patients were stratified by LabScore into three categories with decreasing five-year OS rates: 54.9% versus 38.2% versus 21.6%, respectively. LabScore demonstrated good prognostic performance in both testing (c-index = 0.70) and validation cohorts (c-index = 0.67), outperforming individual lab tests, PNI (c-index = 0.58), and the AJCC staging system (c-index = 0.60). LabScore is a valuable tool to identify patients most likely to benefit from primary surgery and those at high recurrence risk, who might be candidates for neoadjuvant therapy [231].

4.2.4 Pathologic factors

Pathological features were also correlated with postoperative outcomes.

Tumor necrosis was associated with poor prognosis in T1-stage ICC, but not in advanced disease (T2–T3) [232]. Furthermore, Burger et al. [233] found, in a study

of 17 patients with unresectable ICC who were treated with one or more cycles of TACE, that the proportion of tumor necrosis was a better indicator of treatment response than the changes in tumor size (the percentage of tumor necrosis was most strongly associated with improved survival).

Another important determinant of survival is the morphological subtype of ICC. Currently, there are four subtypes of ICC: mass-forming (MF), intraductal growth (IG), periductal infiltrating (PI), and MF with PI components (MF + PI). In patients with the IG-type, OS rates were comparable to those of the MF-type [234], whereas those with PI or MF + PI subtypes had approximately a 45% higher mortality risk compared with MF/IG types [235]. These findings suggest that incorporating tumor morphology into staging systems could improve prognostic precision.

4.2.5 Molecular and immune prognostic factors

Advances in molecular profiling have begun to shed light on the genetic and immune landscape of ICC and its prognostic implications. ICC is a genetically heterogeneous cancer. Common somatic mutations include TP53, KRAS, IDH1/2, ARID1A, BAP1 and gene fusions like FGFR2 fusions [236, 237]. Among these, mutations in TP53 and KRAS stand out as markers of particularly aggressive disease. ICC tumors harboring TP53 or KRAS mutations are associated with a more advanced stage at presentation, higher tumor mutational burden (TMB), and significantly worse survival outcomes [238, 239]. When TP53 and KRAS mutations co-occur, the prognosis is especially poor [240–242]. The BRAF V600E mutation also appears at a more advanced stage and has been linked to resistance to standard chemotherapy, although targeted treatments may offer options in the advanced disease setting [238, 240–242]. In contrast, mutations such as IDH1 or IDH2 (present in a large subset of ICC, especially in non-cirrhotic patients) do not independently worsen prognosis [242–244]. Likewise, Toshida et al. [245] showed that FGFR2 high expression was an independent prognostic factor for recurrence of resected ICC. Another monocenter retrospective study found that patients with ICC and FGFR2 fusions may have a better prognosis than those without FGFR2 alterations in terms of OS and PFS on second-line therapy, but not in first-line systemic therapy [246].

The tumor immune microenvironment of ICC also influences its behavior and, thus, prognosis. TMB is associated with poor differentiation, more aggressive tumor behavior, and increased immunogenicity. Moreover, patients with ICC with high TMB had poor OS and RFS compared to those with low TMB [247, 248]. The pooled data from multiple studies suggest that the expression of PD–L1/PD-1 in the tumor is related to poor OS [249–251].

Other components of the tumor stroma are under investigation. For example, cancer-associated fibroblasts (CAFs) producing IL-6 can create an immunosuppressive niche. High IL-6 in the ICC microenvironment was correlated with early recurrence and chemo-resistance in a series of resected patients [252].

As these molecular and immune factors become better understood, they may inform future prognostic models. While not yet part of routine risk stratification, a time may come when a resected ICC's genomic profile and immune signature help predict its likelihood of recurrence and guide adjuvant therapy choices.

4.2.6 Machine learning and predictive modeling

Machine learning methods were applied to rank prognostic factors and generate subgroups with similar outcomes [253], as well as to develop online calculators and nomograms for estimating long-term survival after ICC resection [189, 254].

In a multi-institutional study, which included 1,146 patients and was published in 2020, a CART model was used to hierarchically associate preoperative risk factors with five-year OS and create homogeneous patient groups. CART identified tumor number and size, ALBI grade, and lymph node imaging appearance (cN status) as the most powerful preoperative predictors of OS. Four prognostic groups were generated – group 1: single ICC ≤5 cm, ALBI grade 1, cN–; group 2: (1) single tumor >5 cm, (2) single tumor ≤5 cm with ALBI grade 2/3, or (3) single tumor ≤5 cm with ALBI grade 1 and metastatic/suspicious LNs (cN +); group 3: two to three tumors; group 4: four or more tumors. Five-year OS rates were 60.5%, 35.8%, 27.5%, and 3.8%, respectively ($p < 0.001$), while five-year DFS rates were 47%, 27.2%, 6.8%, and 0%, respectively ($p < 0.001$). Thus, tumor burden, hepatic functional reserve, and LN status should guide ICC resection candidacy, and the CART model may aid in selecting patients for preoperative systemic or locoregional therapies [255].

Another model is the "clinical staging" model (CS-iCCA) that includes not only the tumor's features but also the patient's factors and serum markers. CS-iCCA combines ECOG performance status, tumor number, tumor size, metastases, albumin, and CA 19-9 levels to stratify patients into four risk groups. One-year OS rates were 87.1%, 72.7%, 48.0%, and 16%, respectively, for CS-iCCA I, II, III, and IV. Concordance indices showed that the new staging system was superior to the current TNM staging system for predicting long-term outcomes [256].

MEGNA is a prognostic scoring system for ICC based on tumor multifocality, extension, grade, lymph node positivity, and age. MEGNA was shown to correlate with survival, with higher scores indicating worse prognosis. It had similar predictive ability to the AJCC eighth edition for OS [257].

The TBS, first developed for HCC, has since been applied to ICC, where it has been proven to be an independent predictor of prognosis. TBS has also been included in several other prognostic scoring systems. For example, the CTC grade, a novel index based on the combination of TBS and CA19-9, is a promising tool for stratifying ICC patients' prognosis following curative resection. Elevated CTC grade is associated with worse prognosis and has been identified as an independent risk factor for poor OS as well as RFS [258]. Likewise, Munir et al. [259] showed that high TBS and high ALBI grade were strongly associated with both early recurrence (88.1%) and five-year risk of death (96.4%).

An online calculator was developed to predict VER (recurrence within six months after ICC resection) based on pre- and postoperative variables. About one-quarter of resected patients experienced VER, which was associated with an extremely poor prognosis (five-year OS was 8.9% in VER vs. 49.8% in non-VER patients; $p < 0.001$). The preoperative model stratified VER risk as follows: low risk (six-month RFS: 87.7%), intermediate risk (six-month RFS: 72.3%), and high risk (six-month RFS: 49.5%; $p < 0.001$) [260]. The postoperative model similarly identified distinct risk cohorts (six-month RFS: 90.0%, 73.1%, and 48.5%, respectively; $p < 0.001$). Both models demonstrated excellent predictive accuracy (C-index: 0.710–0.728 across validation sets). This tool can help clinicians identify patients at high risk of VER, who may benefit from neoadjuvant therapy to avoid futile operations [260].

For resected stage I ICC, Kawashima et al. [261] developed a predictive model that includes CEA, SII, LNM, and tumor size. Based on these parameters, the authors developed an online calculator (https://ktsahara.shinyapps.io/stageI_icc/). According to the above-mentioned parameters, the patients were stratified into three risk groups with significantly different rates of RFS (one-year RFS: low risk – 80.1%, intermediate risk – 60.3%, high risk – 37.7%; $p = 0.001$) [261]. The on-line calculator (based on preoperative data) stratifies patients relative to recurrence risk, helping in decision-making. Patients included in the low-risk group are the main candidates for upfront LR, while those in the high-risk group would benefit from neoadjuvant therapy.

Recurrence rates after curative-intent resection of ICC are very high, with more than half of patients developing recurrence within three years, and the five-year risk of intrahepatic and/or extrahepatic recurrence exceeding 60% (267). In terms of long-term survival (>5 years), only 1 in 10 patients with multiple unfavorable prognostic factors is still alive at five years [262].

Therefore, achieving a cure after ICC resection remains a challenging goal, and future efforts should focus on better understanding ICC carcinogenesis and pathogenesis to identify more effective systemic therapeutic options for this aggressive disease.

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