Journal of Hepatocellular Carcinoma

Dovepress
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REVIEW

Risk Factors for Recurrence in Patients with Hepatocellular Carcinoma After Curative Resection or Ablation

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Abstract: Hepatocellular carcinoma (HCC) is the most common liver cancer and has a high incidence in China, largely due to the high prevalence of hepatitis B virus (HBV) infection. HBV-related HCC often presents with aggressive characteristics but preserved liver function. Resection and ablation are approaches to achieve potentially curative outcomes. However, the recurrence rate is high, with up to 70% within five years. Curative surgery or ablation is used more broadly in China than in Western countries, so identifying patients at high risk of recurrence is essential: risk stratification can inform postoperative management, including surveillance intensity and avoidance of over- or under-treatment. Baseline characteristics provide a simple method of prediction, the impacts of which differ in early and late recurrence. To our knowledge, this is the first narrative review to comprehensively understand the identification, prevalence, and impact of risk factors for both early and late HCC recurrence in Chinese patients following curative-intent resection or ablation. The review suggests that the most impactful risk factors for early recurrence are aggressive tumor features including tumor size, number and vascular invasion. For late recurrence, key risk factors are patient characteristics such as sex, viral infections and liver cirrhosis. As these risk factors are interrelated, several integrated predictive models like nomograms and artificial intelligence (AI) applications have been proposed, which may enhance risk stratification and inform personalized management strategies. These models should be further validated in large prospective studies to achieve clinical application.

Keywords: hepatocellular carcinoma, risk factor, resection, ablation, recurrence, China, HCC

Introduction

Primary liver cancer, most of which is hepatocellular carcinoma (HCC), is a leading cause of cancer-related deaths in China, accounting for approximately 40% of global cases.[1] About 80% of HCC in China are related to hepatitis B virus (HBV).[2] Patients generally have a younger age at diagnosis, larger tumors, and higher rates of portal vein tumor thrombus (PVTT) and extrahepatic metastasis, but better liver function.[2,3] Accordingly, Chinese doctors tend to adopt aggressive treatments. Resection and ablation are key curative intent treatments with broader indications; in addition to early-stage patients, some patients with more advanced HCC are also considered eligible for curative intent therapy in China.[4] However, the postoperative recurrence rate is high, ranging from 30% to 50% in the first two years and increasing to 50% to 70% by five years.[5]

Received: 8 July 2025
Accepted: 7 October 2025
Published: 6 November 2025

To date, there have been no successful Phase 3 studies of adjuvant therapy for HCC. A subgroup analysis of the IMbrave050 study showed recurrence-free survival (RFS) was more favorable in patients beyond "up-to-7" criteria compared to those within the criteria (hazard ratio [HR], 0.84 vs 1.01).[6] Preoperative alpha-fetoprotein (AFP) levels higher than 400 ng/mL, multiple tumors, and a largest tumor diameter greater than 5 cm were significantly associated with overall survival (OS).[6] These findings suggest that higher-risk patients benefit more from adjuvant treatment. Identifying patients at high risk of recurrence is important for study design and clinical management. In particular, inaccurate stratification of recurrence risk may lead to either under- or over-treatment of patients.

Several baseline characteristics have shown strong correlations with recurrence risk in studies. The impact may vary on different populations, etiologies, and recurrence timing. Given the predominant HBV etiology and proactive curative treatments, understanding recurrence risk factors in Chinese HCC patients is crucial for informing surveillance and treatment strategies. To our knowledge, this is the first narrative review to comprehensively understand the identification, prevalence, and impact of risk factors for both early and late HCC recurrence in Chinese patients following curative-intent resection or ablation.

Understanding Early and Late Recurrence

Understanding recurrence patterns is critical for subsequent surveillance, prevention, and treatment. There are two recurrence peaks after resection in HCC. The first occurs 1–2 years with an annual rate of about 23%, then decreasing until 2–3 years. The second is at 4–5 years, with a recurrence rate of approximately 35%.[7] HCC recurrence can be classified into early and late recurrence; however, there is no standardized cut-off with definitions varying between 8 to 24 months.[8–11] Most published studies use one-year or two-year cut-off for classification.

The underlying mechanisms are different. Early recurrence, accounting for over 70%, results from microscopic residual disease due to incomplete tumor removal or intrahepatic metastasis from the primary tumor.[11,12] Late recurrence is associated with the development of *de novo* tumors in patients with ongoing liver disease, especially those with cirrhosis, where the inflammatory and fibrotic environment promotes hepatocarcinogenesis.[11] However, the distinction between early and late recurrence remains unclear, and pathogenetic mechanisms and clinical features may overlap. Genetic sequencing may help differentiate the origins of recurrence, but this is not feasible in clinical practice.

Intrahepatic recurrence is the most common location (~90%) in both early and late recurrence after resection.[7,9,10] Early recurrence has a higher incidence of recurrent extrahepatic metastasis and higher tumor burden.[7,9,10] The prognosis is generally poor with limited subsequent treatment options and the five-year OS rate below 30%.[7–10,13] Patients with late recurrence tend to have a better prognosis and the five-year OS rate exceeding 35% if detected early and managed appropriately.[8–11] For the recurrence pattern after ablation, a study of 222 Chinese HCC patients found 86.5% with recurrence after microwave ablation (MWA) had only intrahepatic tumors within Milan criteria, indicating the potential for receiving curative treatment again.[14] Similarly, patients with early recurrence after MWA experienced shorter OS than those with late recurrence.[14] These findings highlight the importance of close monitoring in the first two years postoperatively.

Risk Factors for Early Recurrence

The prevalence and impact of risk factors for early recurrence in Chinese patients with HCC are summarized in Figure 1 and Tables S1 and 2.

Tumor-Related Factors

Early recurrence primarily results from the aggressive characteristics of the primary tumor. Large tumor size and multiple tumors are significant risk factors following resection. Large tumors are likely to have microvascular invasion (MVI), be multinodular and of low differentiation grade. In multivariate analyses, patients with tumors ≥5 cm have a recurrence risk 1.279–3.96 times higher than those with tumors <5 cm after resection (Table S1). Up to 56.4% of Chinese patients with resectable HCC have a tumor size larger than 5 cm (Table S1). Tumor size >2.6 cm, >3 cm, or >3.5 cm has also been identified as risk factors for early recurrence after resection in some studies.[15–17] Multiple tumors are present in 11.5–36.5% of Chinese HCC patients undergoing resection, with a recurrence risk 1.145–4.30 times higher compared to those with a solitary tumor (Table S1). The presence of satellite nodules preoperatively, reported in 8.1–47.2% of

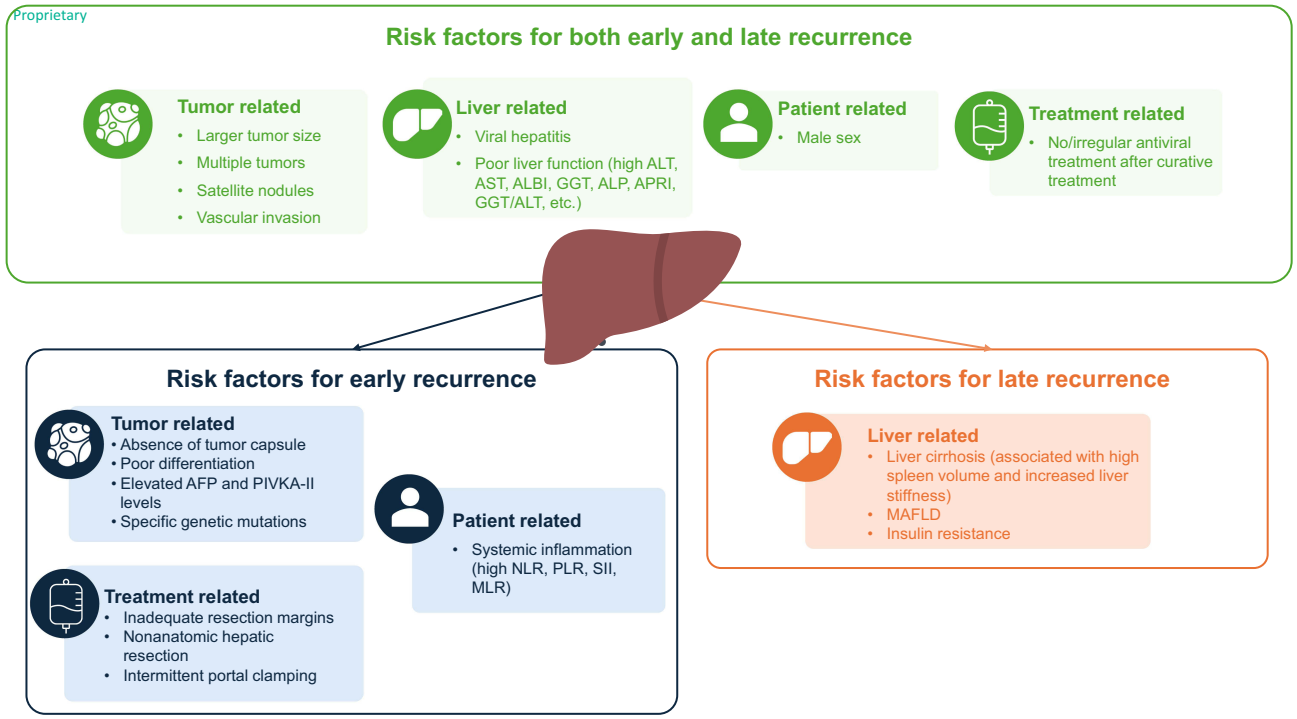

Figure 1 Independent recurrence risk factors for HCC following resection or ablation.
Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, aspartate aminotransferase/platelet ratio index; AST, aspartate transaminase; GGT, glutamyl transpeptidase; HCC, hepatocellular carcinoma; MAFLD, metabolic dysfunction-associated fatty liver disease; MLR, monocyte/lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II; SII, systemic immune-inflammation index.

patients, is associated with a 1.214–2.892-fold recurrence risk after resection (Table S1). Large tumor size and multiple tumors are also linked to early recurrence after ablation (Table S2). Wu et al found larger tumor diameters (HR, 1.24, P = 0.002) and multiple tumor (~19.5% of patients, HR, 1.55, P<0.001) increased early recurrence risk in 513 HCC patients following MWA.[18] Tan et al identified tumor diameter >4 cm (~11.5% of patients) as a risk factor for early progression after radiofrequency ablation (RFA) in 139 early-stage patients (HR, 4.349, P = 0.015).[19] Therefore, the indications for ablation should be limited to single tumors with a small size.

Vascular invasion is a strong predictor of early recurrence, indicating a highly invasive tumor that may form satellite nodules. MVI is reported in 20.2–57.3% of resectable HCC in China (Table S1). Multivariate analyses indicate patients with MVI have a 1.310–8.870 times higher risk of early recurrence than those without MVI (Table S1). M2 has a stronger predictive power than M1 (HR, 3.120, P<0.001).[20] MVI can only be confirmed postoperatively, though imaging features may assist in preoperative prediction.[21] In China, some patients with macrovascular invasion are considered for resection. However, PVTT related intrahepatic micrometastases cannot be completely removed, resulting in a poor 1-year RFS rate of only 13.3%.[22] Macrovascular invasion (3.5–13.7% of patients) is strongly linked to a 1.904–4.472 times higher recurrence risk after resection, highlighting the necessity for perioperative management (Table S1). Other histopathological features, such as poor tumor differentiation (higher Edmondson–Steiner grades) and the absence of tumor capsule, are also predictors of early recurrence after resection or ablation (Tables S1 and S2).

AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) are widely used tumor markers in HCC. Preoperative elevated AFP levels (≥400 ng/mL) are associated with a 1.246–2.91 times higher early recurrence risk after resection compared to lower levels (Table S1). In a study of 751 Chinese patients, PIVKA-II positivity (≥40 mAU/mL) was found in 76.5% of early recurrence cases, compared to 60.0% for AFP positivity (≥20 ng/mL).[23] PIVKA-II and AFP can be complementary for risk evaluation. However, nearly 30% of patients are without elevated tumor markers at baseline, underscoring the need for seeking alternative predictors.

https://doi.org/10.2147/JHC.S552316

Some tumor genetic mutations might indicate the recurrence risk for individuals. In a study of 78 Chinese patients, FH amplification (HR, 3.752, P = 0.026) and RB1 mutations (HR,13.185, P = 0.034) were independently linked to early recurrence.[24] However, baseline biopsy in HCC is not a routine practice, and the relationship of these genes with recurrence requires further validation.

Liver-Related Factors

HBV infection is the leading cause of HCC in China. High preoperative HBV DNA load (>10^4 copies/mL; 54.4% of patients) are linked to aggressive features and increased early recurrence risk (HR,1.557, P<0.001).[7] Hepatitis B e antigen (HBeAg) positivity correlates with shorter RFS (HR, 1.603, P = 0.046) in 203 patients with small tumors following resection.[25] Similarly, hepatitis C virus (HCV) infection (18.2% of patients) also raises the risk of intrahepatic recurrence and multiple recurrent lesions after resection in patients with small HCC.[26] Therefore, perioperative antiviral therapy is crucial to improve clinical outcomes for virus related HCC.

Patients undergoing resection or ablation generally have reserved liver function. Studies found elevated total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) at baseline could predict early recurrence (Tables S1 and 2). High levels may reflect aggressive tumor characteristics and greater tumor cell dissemination. Combined ratios, like the albumin-bilirubin grade, AST/platelet ratio index (APRI), and GGT/ALT (alanine aminotransferase) ratio, may provide more reliable predictors compared to single indicators (Tables S1 and 2).

Patient-Related Factors

Patients related factors also affect early recurrence risk in HCC. Males have a higher likelihood of early recurrence than females after resection (odds ratio, 1.864, P = 0.006).[27] The role of age on prognosis remains inconclusive; some studies showed younger patients (under 40–60 years) at greater risk, while others indicated a 2.66-fold increased risk for older patients (≥ 62 years) (Table S1). Systemic inflammation indicates compromised immune function in cancer patients. Blood cell types such as neutrophils, platelets, and lymphocytes from routine tests can easily reflect the inflammatory status. High ratios of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) are independent predictors of early recurrence in various tumors, including HCC. Hu et al developed the combined systemic immune-inflammation index (SII), finding that a high SII score (>330 × 10^9 cells/L) correlated with vascular invasion, larger tumors, and early recurrence, as well as elevated circulating tumor cell levels.[28] SII also showed superior predictive ability for post-recurrence survival in another study.[29] These inflammation markers offer a simple and low-cost method for monitoring treatment response.

Treatment-Related Factors

Inadequate resection margins may increase the risk of residual tumor cells. A wider resection margin (≥ 1 cm) is generally recommended, but the optimal margin is debated. A randomized study showed that a 2 cm margin reduced multiple tumor recurrences and improved survival compared to a 1 cm margin, especially for HCC tumors ≤ 2 cm, suggesting the extent of resection margin affects recurrence pattern.[30] Nonanatomic hepatic resection may also increase the risk of early recurrence due to micrometastases disseminated via portal venous branches.[31] In addition, Hao et al found intermittent portal clamping to be an independent risk factor for early recurrence, with a lower 2-year RFS rate compared to continuous or no clamping in a study of 266 Chinese patients.[32]

Early recurrence is a major challenge with poor survival in clinical practice. Intensified surveillance and prompt intervention are needed during the first two years after surgery or ablation. Early recurrence is mainly driven by the invasive features of the primary tumor (e.g., multifocality or vascular invasion). Against the backdrop of rapidly evolving systemic and other non-surgical therapies, selection of surgical candidates should be cautious: the benefits of upfront resection or ablation versus alternative curative or combined approaches must be carefully weighed. Various perioperative strategies (such as conversion or neoadjuvant therapies) are being explored in HCC with the aim of improving surgical outcomes. Men, patients with high inflammatory status, or those with poor liver function are at higher risk of early recurrence and require closer follow-up. Meticulous surgical technique aiming for R0 resection with negative

margins is essential. Furthermore, continuous antiviral therapy throughout the treatment course is important and can markedly reduce the risk of early recurrence.

Risk Factors for Late Recurrence

Late recurrence generally results from underlying liver conditions. Risk factors for late recurrence are summarized in Figure 1 and Tables S3 and 4.

Liver-Related Factors

Liver-related factors significantly impact late recurrence in HCC. Chronic HBV infection is a major risk factor in Chinese patients. Clonal integration of HBV DNA into the host genome, together with hypermethylation of tumor suppressor gene promoters, promotes hepatocarcinogenesis and directly increases the risk of de novo tumors.[33–35] Studies of Chinese patients showed active HBV replication (HBV DNA $>10^4$ copies/mL, HR, 1.557, P<0.001) and positivity for HBeAg (HR, 2.186, P = 0.023) preoperatively were associated with an increased risk of both early and late recurrence.[7,25] Liver cirrhosis or fibrosis (66.6–78.2% of patients) significantly increases the risk of de novo HCC and late recurrence after resection (HR, 1.302–6.738) and ablation (HR, 4.321, P = 0.049) (Table S4).[36] Cirrhosis-related factors like high spleen volume (>370 cm^3 or ≥165 mL) and high liver stiffness (>3.62 kPa or >8.5 kPa) can also predict late recurrence (Table S3).

Liver function indicators are also associated with late recurrence risk. Zhang et al found a high APRI (>0.78) in 32.6% of Chinese patients undergoing RFA significantly predicted late recurrence (HR, 6.221, P<0.001).[37] Similarly, Liu et al reported a APRI >0.23 (65.9% of patients) increased late recurrence risk after resection (HR, 2.018, P = 0.030).[38] High ALT, AST, and ALP are also linked to elevated late recurrence risk (Tables S3 and 4).

In addition, metabolic associated fatty liver disease (MAFLD)-related HCC is increasing in China. Studies have shown that MAFLD raises the risk of late recurrence after resection due to persistent inflammation, insulin resistance, and cirrhosis.[39–41] Mechanistically, the TGF-β/SMAD signaling pathway has the potential to interact with the development of cirrhosis in MAFLD.[42,43] Lifestyle changes to improve insulin resistance may reduce recurrence.

Tumor-Related Factors

While less influential than for early recurrence, primary tumor characteristics such as size, number, and vascular invasion also affect the late recurrence risk. Studies of Chinese patients undergoing resection showed that tumors ≥5 cm significantly increase late recurrence risk (HR, 1.305–2.51), along with multiple tumors (HR, 1.462–10.05) and satellite nodules (HR, 1.347–2.051) (Table S3). Similar impacts are observed in patients undergoing ablation (Table S4). Vascular invasion including microvascular (HR, 1.381–1.686) and macrovascular invasion (HR, 2.661–5.480) are also related with late recurrence following resection (Table S3).

Patient-Related Factors

Sex disparities are also observed in late recurrence. Wang et al studied 894 Chinese patients with HBV HCC undergoing resection and found male patients had a higher risk of late recurrence (HR, 1.750, P = 0.043).[7] More attention should be paid to male patients during long-term surveillance.

Late recurrence is mostly related to patient factors such as impaired liver function, chronic hepatitis, or underlying cirrhosis. Long-term, regular follow-up is required to detect recurrence early, with particularly close monitoring for men and those whose baseline tumors show high invasiveness. For Chinese patients with HCC, standardized antiviral therapy for HBV is essential to reduce viral liver injury and lower recurrence risk. With the rising prevalence of MAFLD, lifestyle interventions should also be emphasized as an important strategy to prevent late recurrence.

Integrated Risk Models

So far, there is broad consensus on several major risk factors for early and late recurrence in HCC across different regions. However, tumor recurrence is a complex process where various risk factors are interconnected. Integrating these

factors may improve prediction accuracy, as demonstrated in several phase 3 adjuvant treatment trials for risk stratification (Table 1). Additionally, predictive models that integrate clinicopathological and radiomics features are proposed.

Liu et al developed the Preoperative Very Early Recurrence Model (VERM-pre) to predict 1-year recurrence rates using eight baseline variables: tumor diameter, number, AFP, macrovascular invasion, satellite nodules, HBV DNA levels, GGT, and prothrombin time.[48] The model was validated in 7401 Chinese patients with high discrimination capacity to stratify patients into three risk groups. Sun et al developed the "Shanghai Score" using 14 clinical and

Table 1 The Reported High-Risk Screening Criteria in Key Phase 3 Trials on HCC Adjuvant Therapies

Study	Setting	High-Risk Factors	Treatments	RFS	OS
STORM[8] (NCT00692770)	HCC after resection or ablation	**Resection** **High risk**: • single tumor with MVI, satellite tumors or poorly differentiated • 2–3 tumors, each ≤3 cm **Intermediate risk**: • single tumor ≥2 cm with moderate or well-differentiated; without MVI or satellite tumors **Ablation** **High risk**: • single tumor 3–5 cm • 2–3 tumors, each ≤3 cm **Intermediate risk**: • single tumor 2–3 cm	Sorafenib vs placebo	33.3 vs 33.7 mo; HR 0.940 (95% CI, 0.780, 1.134)	NR vs NR HR 0.995 (95% CI, 0.761, 1.300)
TACE[44] (NCT01966133)	HBV HCC after resection	**High risk**: • single tumor with MVI • 2–3 tumors **Intermediate risk**: • single tumor > 5 cm without MVI	TACE vs surveillance	49.5 vs 23.8 mo P=0.01	NR vs NR P=0.04
HAIC[45] (NCT03192618)	HCC with MVI after resection	MVI	HAIC vs surveillance	20.3 vs 10.0 mo HR 0.59 (95% CI, 0.43, 0.81)	3-year OS rate: 80.4% vs 74.9%
IMbrave050[46] (NCT04102098)	HCC after resection or ablation	**Resection** • ≤3 tumors, the largest >5 cm, or poor differentiation (grade 3 or 4) • ≥4 tumors, the largest ≤5 cm or poor differentiation (grade 3 or 4) • ≤3 tumors, the largest ≤5 cm with vascular invasion (microvascular or Vp1 or Vp2) **Ablation** • single tumor >2 cm but ≤5 cm • multiple tumors (< 4), all ≤5 cm	Atezolizumab plus bevacizumab vs surveillance	Updated results: 33.2 vs 36.0 mo HR 0.90 (95% CI, 0.72,1.12)	Updated results: NR vs NR HR 1.26 (95% CI, 0.85,1.87)
KEYNOTE 937[47] (NCT03867084)	HCC after resection or ablation	• Single tumor 2–3 cm • 2–4 tumors, all ≤3 cm or single tumor > 3 cm but ≤5 cm • 2–4 tumors with at least one > 3 cm and all ≤5 cm	Pembrolizumab vs placebo	Not published	Not published

(*Continued*)

Table 1 (Continued).

Study	Setting	High-Risk Factors	Treatments	RFS	OS
CheckMate 9DX[47] (NCT03383458)	HCC after resection or ablation	**Resection** • ≤3 tumors, at least one > 5 cm, no macrovascular invasion • ≤3 tumors, all≤5 cm but with microvascular invasion (no macrovascular invasion) or grade 3/4 tumor • > 3 tumors, all≤5 cm and no macrovascular invasion **Ablation** • single tumor > 3 cm but ≤5 cm • multiple tumors (≤4), all≤5 cm	Nivolumab vs placebo	Not published	Not published

Abbreviations: HCC, hepatocellular carcinoma; RFS, recurrence-free survival; OS, overall survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; Mo, months; MVI, microvascular invasion; NR, not reached.

laboratory variables for postoperative stratification.[49] Additionally, radiomic features have also been integrated into models to enhance the accuracy.[50] Emerging technologies like artificial intelligence (AI) can automatically extract quantitative clinical and imaging features and analyze the complex relationships between these features and clinical outcomes, which might change the workflow in future. A study involving 4758 patients compared an AI based radiomics model with traditional Cox models. The AI-based model significantly outperformed the others in risk stratification (all $P<0.0001$).[51]

Models like the age-male-albumin-bilirubin -platelet (aMAP) score and APRI score, initially designed to predict HCC development in chronic liver disease patients, can also be useful for predicting late recurrence. Yang et al developed a nomogram based on the aMAP score and tumor number that effectively stratified 339 patients undergoing RFA into low, medium, and high-risk groups, achieving strong predictive accuracy for 3-, 4-, and 5-year RFS.[52]

Currently, there is no globally recognized predictive model. Further trials are needed to evaluate the validity, accuracy, reproducibility, and management impact of these models before widespread clinical application.

Future Directions and Review Limitations

HBV predominates in China and is associated with higher recurrence, whereas HCV and MAFLD are more common in the West, with more advanced cirrhosis and comorbidities. Broader indications for surgery and ablation in China likely increase recurrence rates and underscore the need for more accurate risk stratification. Relying solely on clinical characteristics is a simple method to predict prognosis. Combining postoperative status or applying new technologies can comprehensively assess patients and provide timely insights for perioperative management. Emerging evidence suggests that liquid biopsy techniques, such as detecting circulating tumor DNA mutations or methylation patterns, are promising noninvasive methods to predict recurrence and monitor tumor burden in HCC.[53] This approach has demonstrated greater accuracy in some cancers.[54] With a deeper understanding of recurrence mechanism in HCC, future studies can consider integrating genomic, transcriptomic, and proteomic data to achieve more precise patient stratification. In addition, there are urgent medical needs to explore effective and safe treatment regimens in the perioperative setting.

There are some limitations in this review. Most independent risk factors are identified from retrospective studies. The included studies exhibited heterogeneity in population selection and follow-up intervals, resulting in varying thresholds and proportions of patients for the same risk factors across studies. In addition, the review focus on Chinese HCC with dominant HBV infection, which limits the generalizability of the results to other populations with different etiologies. Moreover, the absence of standardization in defining and detecting early and late recurrence may result in inconsistent findings across studies. These issues require prospective validation studies for answers, and standardizing the population and definitions is essential for further studies.

Conclusions

Understanding the recurrence risk factors is crucial to tailor surveillance and treatment strategies for HCC patients following curative resection or ablation. Baseline characteristics including tumor, liver, and patient-related factors provide a simple method to predict recurrence with distinct patterns for early and late recurrence and inform patient selection. However, most reported independent risk factors were derived from retrospective studies and require validation in large, multicenter prospective cohorts. The key recurrence risk factors are generally interrelated and multiple prediction models that integrate clinical, imaging, pathological data and even novel techniques such as liquid biopsy and AI are developed with the aim to improve prediction capability. These models also need be validated in large prospective studies to achieve clinical application. Meanwhile, effective preventive therapies to reduce recurrence are urgently needed.

Acknowledgments

Medical writing support was provided by Phoebe Kennedy, MSc, and Jake Burrell, PhD at Rude Health Consulting Ltd.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This review was funded by MSD China.

Disclosure

Xiaodong Zhu has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from BeiGene, Eisai, Innovent, MSD, Roche and Hengrui Pharma. Dantong Cheng and Xijie Zhang are employed by MSD China. The other authors have no competing interests to declare.

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