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Editorial

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Expert consensus on sequential surgery after immune-targeted conversion therapy for advanced hepatocellular carcinoma in China

Peipei Song, Wei Tang*, Norihiro Kokudo

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SUMMARY Hepatocellular carcinoma (HCC) represents a significant global health burden, particularly in the Asia-Pacific region, where it is a leading cause of cancer-related mortality. In China alone, HCC accounts for approximately 367,700 new cases and 316,500 deaths annually; over 50% of patients are diagnosed at an advanced stage, limiting curative treatment options and resulting in poor survival outcomes. Systemic therapies combining immune checkpoint inhibitors (ICIs) with antiangiogenic targeted drugs have shown promise in converting unresectable HCC into resectable cases, potentially transforming clinical outcomes. The Chines expert consensus on sequential surgery following conversion therapy based on combination of immune checkpoint inhibitors and antiangiogenic targeted drugs for advanced hepatocellular carcinoma (2024 edition) provides an updated, multidisciplinary framework emphasizing sequential surgery post-conversion therapy. The consensus highlights treatment protocols, efficacy evaluation, and innovative adjuvant strategies to refine clinical practice and enhance survival outcomes in advanced HCC.

Keywords hepatocellular carcinoma (HCC), immuno-targeted conversion therapy, sequential surgery

Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy and a leading cause of cancer-related deaths globally, with a disproportionate burden in the Asia-Pacific region (*1*). In China alone, HCC accounts for approximately 367,700 new cases and 316,500 deaths annually. Unfortunately, over 50% of patients are diagnosed at an advanced stage, limiting curative treatment options and resulting in poor survival outcomes (*2,3*).

From an international perspective, China's approach to the diagnosis and treatment of HCC, especially in the management of advanced HCC and the advancement of diversified treatment options, is of significant importance. It not only helps improve patient prognosis but also provides valuable insights for clinical research and practice worldwide.

Globally, advances in systemic therapies, particularly immuno-targeted approaches combining ICIs with antiangiogenic drugs (AATDs), have dramatically reshaped the treatment paradigm for advanced HCC(*4-6*). These combination therapies improve response rates and survival, enabling successful downstaging and conversion therapy. The potential for sequential surgeries following such conversion therapy has emerged as a pivotal strategy, offering radical resection opportunities and long-term survival benefits (*2,3*).

In China, the 2024 edition of the Chines expert consensus on sequential surgery following conversion therapy based on combination of immune checkpoint inhibitors and antiangiogenic targeted drugs for advanced hepatocellular carcinoma developed through collaboration among leading hepatology and oncology experts, marks a significant step forward. It builds upon prior iterations to establish a robust protocol for managing advanced HCC, including conversion therapy strategies, sequential surgery guidelines, and tailored adjuvant treatments based on resected specimen pathology (*2*).

The consensus introduces objective and practical criteria for treatment efficacy, emphasizing imaging and tumor markers. It also highlights the role of multidisciplinary teams in optimizing patient outcomes. Innovations in local and systemic therapies are harmonized, ensuring safe and effective transitions from conversion therapy to surgical interventions.

The consensus aligns with the broader goals of the Healthy China 2030 initiative to improve cancer care and achieve a 15% increase in overall 5-year survival rates for liver cancer (*7*). While primarily intended for the high-burden HCC population in China, its recommendations

provide a framework applicable to global clinical practice, offering hope for a transformative impact on advanced HCC treatment worldwide.

By integrating advanced systemic therapies with multidisciplinary surgical strategies, the consensus in China provides a comprehensive framework for managing this complex malignancy. This approach lays the foundation for improving both survival outcomes and the quality of life for patients with advanced HCC in China, and can serve as a valuable reference for clinical practice and research worldwide.

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Editorial

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Applications of and issues with machine learning in medicine: Bridging the gap with explainable AI

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SUMMARY In recent years, machine learning, and particularly deep learning, has shown remarkable potential in various fields, including medicine. Advanced techniques like convolutional neural networks and transformers have enabled high-performance predictions for complex problems, making machine learning a valuable tool in medical decision-making. From predicting postoperative complications to assessing disease risk, machine learning has been actively used to analyze patient data and assist healthcare professionals. However, the "black box" problem, wherein the internal workings of machine learning models are opaque and difficult to interpret, poses a significant challenge in medical applications. The lack of transparency may hinder trust and acceptance by clinicians and patients, making the development of explainable AI (XAI) techniques essential. XAI aims to provide both global and local explanations for machine learning models, offering insights into how predictions are made and which factors influence these outcomes. In this article, we explore various applications of machine learning in medicine, describe commonly used algorithms, and discuss explainable AI as a promising solution to enhance the interpretability of these models. By integrating explainability into machine learning, we aim to ensure its ethical and practical application in healthcare, ultimately improving patient outcomes and supporting personalized treatment strategies.

Keywords machine learning, deep learning, explainable AI, medical applications

1. Introduction

In recent years, machine learning technologies, and particularly deep learning (*1*), have advanced rapidly. The emergence of techniques such as convolutional neural networks (*2,3*) and transformers (*4*), which are designed for image recognition and natural language processing, has enabled high-performance predictions even for complex problems. While terms like "deep learning" and "artificial intelligence (AI)" have gained popularity recently, these technologies are part of a broader category of machine learning. Machine learning is a technique where algorithms, using data, discover and learn patterns and features from that data and make predictions or classifications based on the learned results. A key feature of machine learning is that, instead of humans manually defining rules for predictions (*e.g.*, if a measurement is above 1, classify as A, otherwise classify as B), the algorithm itself identifies patterns from the collected data and its corresponding outcomes. By finding regularities within large datasets, machine learning enables accurate predictions. As machine learning technology has progressed, its applications have expanded to various fields, including medicine, where research utilizing machine learning is actively being conducted.

In the medical field, machine learning holds great potential. It has been used to predict postoperative outcomes based on patient measurements (*5,6*) and disease risk (*7*). The realization of predictive models using machine learning is expected to significantly contribute to the decision-making of medical professionals and to the treatment of patients. Despite its high potential for medical applications, machine learning faces a significant challenge in the form of the "black box" problem. The black box problem refers to the issue where the prediction results and processes generated by machine learning are not easily understandable by humans. As machine learning algorithms become more complex, their behavior becomes more difficult to interpret at a macro level, even though some aspects may be understood at a micro level. This complexity leads to situations where why a certain prediction was made or the thought process that underpinned it is unclear. This lack of transparency can be a major barrier to the acceptance of machine learning in the medical field,

as physicians and patients may be reluctant to trust predictions with a rationale that is not clear.

A technology known as Explainable AI (XAI) (*8,9*) has been gaining attention as a way to address the black box problem. XAI involves analyzing machine learning models to clarify how predictions are made, identify trends in predictions, and provide reasoning for those predictions. By presenting the importance of various features in a manner that is understandable to humans, XAI helps to reveal the factors influencing the algorithm's outcomes. As a result, it should make machine learning more acceptable in the medical field.

The current study starts by presenting specific examples of medical applications of machine learning. Next, the mechanisms behind commonly used machine learning algorithms are described. Last, this study provides an in-depth explanation of explainable machine learning techniques as a solution to the black box problem. Through this discussion, we aim to share insights into the potential applications of machine learning in the healthcare field.

2. Machine learning applications in the medical field

With the rapid advancement of AI and deep learning in recent years, research utilizing machine learning for disease prediction, diagnosis, and prognosis prediction has been widely conducted in the medical field. These models are expected to analyze complex patient data and serve as tools to predict complications, recovery outcomes, and aid in decision-making with regard to treatment strategies. Here, we will describe specific examples of medical applications of machine learning that are anticipated to contribute to medical decision-making.

2.1. Prediction of Postoperative Complications

Machine learning is highly effective in predicting the risk of postoperative complications (*5*). For example, models have been proposed to assess the risk of severe postoperative complications such as pneumonia, acute kidney injury, deep vein thrombosis, and pulmonary embolism. By using data from 111,888 surgeries (including patient characteristics and clinical information), five different ML algorithms (logistic regression (*10*), support vector machine (SVM) (*11*), random forest (*12*), gradient boosting (*13*), and deep neural networks) were used to compare the accuracy with which postoperative complications were predicted. Results demonstrated that the combination of preoperative and intraoperative data provided the highest prediction accuracy, highlighting the effectiveness of machine learning as a tool for postoperative risk management.

2.2. Early prediction of diabetes and cardiovascular diseases

Machine learning models are also effectively utilized to predict diabetes and cardiovascular diseases (*7*). These models integrate a variety of data, such as family history, age, weight, blood pressure, cholesterol levels, and lifestyle habits (*e.g.*, smoking and exercise), to predict disease risk. Studies have constructed models using algorithms suited for linear relationships, such as linear regression and SVM, as well as algorithms that account for nonlinear relationships, like random forest and gradient boosting, to provide highly accurate predictions.

2.3. Prediction of postoperative outcomes

Machine learning has been used to predict postoperative outcomes. A study sought to predict four short-term adverse events – extended hospitalization, discharge to a location other than home, readmission within 30 days, and major complications – following anterior cervical discectomy and fusion surgery (*6*). The study explored model construction using five machine learning algorithms: TabPFN (*14*), TabNET (*15*), XGBoost (*16*), LightGBM (*17*), and Random forest. Random forest demonstrated the best performance of the five, with an AUROC ranging from 0.776 to 0.846. Estimating the risk of postoperative adverse events enables early personalized interventions for each patient, helping to manage a potential deterioration in their condition.

As demonstrated, various predictive studies using clinical data have been conducted. Table 1 summarizes additional studies related to the application of machine learning in the medical field, including the algorithms used and their purposes. Traditional techniques like linear regression and logistic regression were limited to linear problems. However, with the advancement of machine learning and improvements in the learning and predictive performance of various algorithms, these models can now be applied to more complex problems.

3. Representative machine learning algorithms commonly used in recent years

In the field of machine learning, various algorithms have been developed and are widely used. Among these, foundational and representative methods that can be used for classification and prediction include logistic regression, decision trees (*18*), random forest, gradient boosting, SVM, and deep learning. Logistic regression and decision trees are simple in their configuration and easy to interpret, but their predictive accuracy is relatively low. In contrast, algorithms such as gradient boosting and deep learning exhibit superior predictive performance, though they are more difficult to interpret.

3.1. Logistic regression

Logistic regression (*10*) is a commonly used algorithm in the medical field and is one of the fundamental

algorithms in machine learning. It is particularly well-suited for binary classification tasks and operates similarly to linear regression. Logistic regression performs a weighted linear combination of the input explanatory variables and passes the result through a sigmoid function to predict probabilities between 0 and 1. The weights are parameters calculated based on the training data, and effectively determining these parameters enables predictive tasks to be performed. This process is known as learning. Simply put, learning involves finding the parameters of a function that can accurately represent the relationship between the observed explanatory variables and the target variable. This learning step is achieved through optimization techniques.

In optimization, a loss function is defined to represent the objective that needs to be minimized, and the parameters are adjusted to minimize this function. In logistic regression, the goal is to maximize the log-likelihood, which is transformed into a form that minimizes the loss function. Through this optimization, logistic regression finds the most plausible parameters that fit the characteristics of the training data, allowing it to make predictions for binary classification tasks. Logistic regression assumes that the problem is linearly separable, so it may not perform well when there is a nonlinear relationship between the explanatory and target variables. The simplicity of logistic regression, along with the interpretability provided by the weighting of each explanatory variable, has resulted in its widespread use in the medical field.

3.2. Decision trees

Like logistic regression, decision trees (*18*) are intuitive and easy-to-interpret machine learning algorithms. A decision tree classifies input data by recursively splitting it according to specific rules. The structure formed by these splits resembles a tree, as shown in Figure 1, which is why it is called a decision tree. Figure 1 illustrates a tree structure that predicts whether the temperature on a given day will exceed 22°C based on inputs such as weather and season. In this tree structure, the path is determined from the top of the tree, based on the values of the input data. If, for example, the weather is sunny, the model follows the path on the right, while if the weather is cloudy or rainy it follows the path on the left. This process is repeated until the model predicts whether the temperature will exceed 22°C. Constructing a tree structure that accurately represents the data is essential, and algorithms such as ID3 (*18*), CART (*19*), and C4.5 (*20*) have been proposed for this purpose.

A key strength of decision trees is that the tree structure clearly shows the criteria for making predictions and which features are used, making the model easy to interpret. Unlike logistic regression, decision trees can be applied to non-linear problems. However, decision trees are prone to overfitting, meaning that they may perform too well on the training data, resulting in poor performance on unseen data.

3.3. Random forest

Random forest (*12*) is an algorithm that improves prediction accuracy by combining multiple decision trees. While individual decision trees are prone to overfitting and may exhibit low predictive performance, a random forest generates multiple decision trees and aggregates their predictions to enhance accuracy. The term "forest" refers to the collection of decision trees. This approach of combining weak predictors – multiple decision trees – to improve overall performance is called ensemble learning. A random forest operates in three main steps: bootstrap sampling, decision tree construction, and prediction aggregation.

In the first step, bootstrap sampling, the training data are divided into several sub-datasets. In the second step, decision trees are constructed for each sub-dataset using randomly selected subsets of input features. By randomly sampling the features, each decision tree learns from a different combination of variables, increasing the diversity of the trees and helping to prevent overfitting. In the third step, the predictions from the various decision trees are aggregated, either through majority voting or by averaging, to make the final prediction. A random forest offers higher accuracy and is less prone to overfitting compared to individual decision trees. However, a disadvantage of this approach is that the model is more difficult to interpret. While a single decision tree can be easily understood, interpreting how the different variables interact to produce the final prediction is challenging when multiple trees are combined.

3.4. Gradient boosting

Gradient boosting (*13*) is another type of ensemble learning that combines multiple weak predictors (usually decision trees) to build a strong model. While a random forest aggregates the predictions of multiple decision trees, gradient boosting takes a different approach by sequentially creating decision trees, where each new tree is trained to correct the errors made by the previous ones. The process starts by creating an initial decision tree, which typically results in significant errors between the predicted values and the actual data. To address this, the errors between the predicted results and the actual values are calculated. A new decision tree is then trained to predict these errors. Combining the outputs of the initial tree and the subsequent tree, which focuses on correcting mistakes, improves the overall performance of the model.

This process of error correction is repeated, allowing the model to refine itself and reduce prediction errors

Table 1. Overview of Studies Applying Machine Learning in the Medical Field

Study	Machine Learning Algorithms Used	Prediction Performance
Prediction of Acute Kidney Injury after Cardiac Surgery (*24*)	Logistic Regression, SVM, Random Forest (RF), XGBoost, RF + XGBoost	Area Under the Curve (AUC): 0.843 (RF + XGBoost)
Prediction of Postoperative Complications (Pneumonia, AKI, DVT, *etc.*) (*5*)	Gradient Boosting, Deep Neural Network (DNN), RF, SVM	AUC: 0.905 (Gradient Boosting)
Prediction of Acute Kidney Injury after Aortic Arch Surgery (*25*)	Logistic Regression, SVM, RF, Gradient Boosting	AUC: 0.8 (Gradient Boosting)
Risk Prediction of Diabetes and Cardiovascular Diseases (*7*)	Logistic Regression, SVM, RF, Gradient Boosting	AUC: 0.862 (XGBoost)
Prediction of Postoperative Outcomes (*6*)	TabPFN, TabNET, XGBoost, LightGBM, RF	AUC: 0.776 (RF)
Prediction of 30-day Postoperative Mortality Risk (*26*)	Convolutional Neural Network (CNN), DNN, RF, SVM	AUC: 0.867 (CNN)
Prediction of Postoperative Delirium (POD) in Elderly Patients (*27*)	Logistic Regression, RF, GBM, XGBoost, Ensemble	AUC: 0.783 (Logistic Regression)
Prediction of Mortality Risk after Hepatocellular Carcinoma Surgery (*28*)	Logistic Regression, RF, Gradient Boosting, Decision Tree	AUC: 0.803 (RF)
Prediction of Postoperative Survival in Gastric Cancer Patients (*29*)	Cox Regression, Random Survival Forest, DNN	AUC: 0.868 ((DNN)
Prediction of ICU Admission and 30-day Postoperative Mortality Risk (*30*)	RF, Gradient Boosting, SVM, Adaptive Boosting	AUPRC: 0.38 (Gradient Boosting)

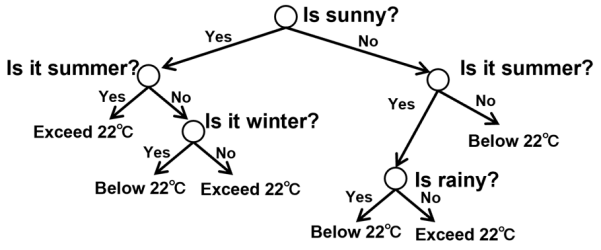

Figure 1. Sample decision tree with splits and nodes. This decision tree demonstrates how inputs such as season and weather conditions are used to predict whether the temperature will exceed 22°C. The tree branches represent the decision-making process, splitting based on the input features to arrive at a final prediction.

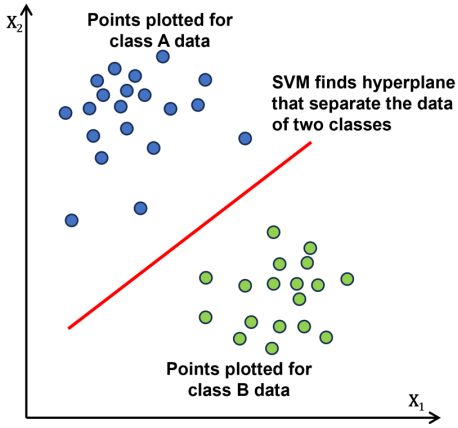

Figure 2. Hyperplane separation of two classes using a support vector machine (SVM). A SVM identifies the optimal hyperplane that maximizes the margin between the two classes.

with each iteration, ultimately resulting in a high level of predictive accuracy. Popular algorithms that implement gradient boosting include XGBoost (*16*) and LightGBM (*17*), which have been optimized for both performance and computational efficiency. This makes them suitable for large-scale datasets. Gradient boosting often produces more accurate models compared to decision trees and is less prone to overfitting. However, similar to a random forest, the combination of multiple decision trees makes interpreting how the model arrived at its predictions difficult, posing challenges in understanding the rationale behind the results.

3.5. SVM

SVM (*11*) is a powerful machine learning algorithm used for classification and regression problems. It works by finding an optimal boundary that separates the classes in the training data, which is then used to make predictions. For example, as illustrated in Figure 2, a dataset with two variables, X and Y, is plotted. The data belong to two classes (A and B), and each class is grouped within a certain region in a two-dimensional space. SVM finds the optimal boundary that best separates the two classes in this space. When new piece of data is plotted, if it falls on the side of the boundary corresponding to

class A, it is predicted to be class A, and if it falls on the side corresponding to class B, it is predicted to be class B. While this example involves two variables and two dimensions, SVM can be extended to handle higher-dimensional data by increasing the number of explanatory variables.

Initially, SVM was designed for linear problems, but the algorithm has been improved to handle nonlinear problems as well. Linear problems are relatively easy to interpret, but interpretation becomes more challenging when dealing with nonlinear problems.

3.6. Deep learning

Deep learning (*1*) is a model that mimics the behavior of neurons in the brain, using artificial neurons as mathematical models. An artificial neuron receives inputs from explanatory variables, applies a weighted linear combination, and passes the result through an activation function, with the output serving as the neuron's response. If a sigmoid function is used as the activation function, this operation is nearly identical to logistic regression. In deep learning, as shown in Figure 3, multiple artificial neurons with the same input variables are constructed and treated as layers in a neural network. The output of one neural network layer is then used as the input for another, with multiple layers connected to form a full neural network. Each artificial neuron has weight parameters used in its computations, and adjusting these weights enables the neural network to achieve superior predictive performance.

The parameters are determined through training with data. Initially, random values are assigned as weights, and the output of the neural network is calculated based on the input data. The error between the predicted output and the actual values is then calculated, and the weights are adjusted to reduce the error. This process is repeated multiple times, gradually refining the parameters so that the network can accurately predict the correct output when given new input data. Conceptually, this can be viewed as a model composed of multiple connected logistic regression models.

Over the past decade, deep learning has been intensively researched, leading to various improvements and new network structures that have resulted in higher performance compared to other models. In particular, convolutional neural networks (*3*) for image recognition have gained prominence, while transformers have emerged for language processing and time-series analysis, with extensive research being conducted in these areas.

4. Explainable machine learning

Thus far, we have described representative machine learning algorithms. While each algorithm has its strengths and weaknesses, they all demonstrate a high level of performance. However, there is a significant challenge when applying these algorithms to the medical field: interpretability. Algorithms like logistic regression and decision trees are simple, making their predictions relatively easy to interpret. However, the more advanced algorithms developed in recent years, which exhibit excellent performance, are more complex and difficult to interpret, leading to a "black box" problem. Although the individual operations performed by the models can be understood at a micro level, interpreting the model as a whole is difficult. This challenge is known as the black box problem, and it is a significant issue in fields like medicine, where rationales for and explanations of diagnoses are especially important.

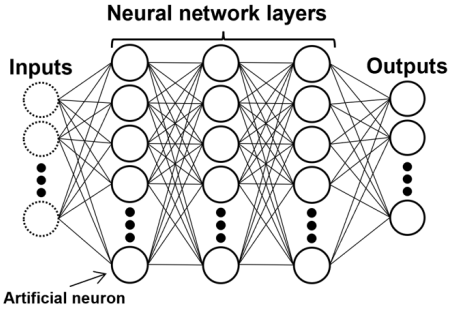

Figure 3. Conceptual Structure of Neural Networks. Each circle represents an artificial neuron that receives inputs from the preceding layer, applies a weighted linear combination, and passes the result through an activation function. Multiple layers of neurons are shown, where the output of one layer becomes the input to the next, forming a deep network.

To address the black box problem, efforts are underway to develop technologies that can explain the internal structure and decision-making processes of models in a way that humans can understand. These technologies are collectively referred to as XAI, and several approaches are emerging in this area (*8,9*). XAI primarily attempts to explain machine learning models from two perspectives: global and local explanations.

4.1. Global explanations

Global explanations aim to describe the overall characteristics of the model itself. A machine learning model learns from training data to obtain parameters and a structure that allows it to perform predictive tasks. By analyzing which explanatory variables the model emphasizes when making predictions, a technique called Feature Importance can be used to calculate and assess which variables are most important to the model. Another global interpretability approach involves constructing a simplified model that is easier to interpret and using that model to understand the behavior of the more complex model. For example, a simplified interpretable model, such as a decision tree or logistic regression, can be used to approximate the behavior of a deep learning model. The deep learning model, seen externally, functions as

Table 2. Summary of Explainable AI Techniques*

Explanation Type	Method/Technique	Description	Use Case
Global Explanation	Feature Importance	Evaluates which variables the model emphasizes for prediction and identifies important ones.	Analyzing how certain features impact predictions across the model.
	Surrogate Models (decision trees, logistic regression)	Simplifies complex models (*e.g.*, deep learning) by approximating them with interpretable models like decision trees or logistic regression.	Using a simple model to explain the behavior of complex models.
Local Explanation	Shapley Additive Explanations Local Interpretable Model-agnostic Explanations	Provides a local explanation by showing which features contributed and how much to a specific prediction.	• Understanding key factors for predicting based on input data. • Helping a physician understand why a specific prediction was made for a patient.
	Influence Functions	Calculates how individual training samples influenced a specific prediction.	Identifying which past cases in training data most influenced a given diagnosis.

*The methods are categorized into global explanations, which provide insights into the overall behavior of a model, and local explanations, which offer case-specific rationales for individual predictions.

a predictor that outputs some result when given input data. By collecting the outputs from various inputs and using these data to train a decision tree, the tree will approximate the behavior of the deep learning model. The decision tree can then be visualized, helping to explain why certain outputs are predicted based on specific input variables. This type of global explanation can help identify important explanatory variables and can be used to improve models. Moreover, if the explanations provided by the model align with existing research, this can enhance the model's validity and credibility.

4.2. Local explanations

Local explanations, in contrast, provide insights into specific predictions made by the model when given particular input data. For instance, if a machine learning model predicts the presence or absence of a disease based on electronic health record data, a physician might have difficulty understanding why the model predicted that the patient has the disease or why it predicted that the patient does not. Local explanations provide explanations for these individual cases. There are several methods of providing local explanations, but two commonly used approaches are described here. One method identifies the main factors that contributed to the prediction. If, for example, a model predicts that a patient has diabetes, XAI might indicate that blood sugar levels and hemoglobin in the electronic health record were particularly high, indicating which factors the model considered important. XAI techniques like Shapley Additive Explanations (SHAP) (*21*) and Local Interpretable Model-agnostic Explanations (LIME) (*22*) are used to achieve this. Another approach involves finding similar past cases to provide an explanation. If, for example, a model predicts that a patient has diabetes, XAI might search through the training data to find similar cases and present a rationale such as "the selected patient was also diagnosed with diabetes under similar conditions". Influence Functions (*23*) are often used to provide these explanations. Influence Functions calculate how much each training sample contributed to a given prediction. Applying this method to the mode enables determination of which training data samples were most influential in shaping the model. By reviewing the most influential samples that relate to diabetes, one can understand which past data the model relied on when making its prediction. Influence Functions can also be used to improve models by identifying abnormal data that disproportionately influence the model's predictions. Such data might represent outliers.

Therefore, XAI techniques are being proposed to provide both global and local explanations, and they are being used to improve the interpretability of machine learning models. Table 2 summarizes the XAI methods discussed thus far. While XAI is still an evolving field, it is steadily providing a foundation for offering rational explanations, addressing the black box problem, and facilitating the practical use of machine learning in the medical field.

5. Conclusion

Thanks to the advent of deep learning in particular, machine learning has demonstrated great potential in various fields, including medicine. Its ability to analyze large, complex datasets and make accurate predictions offers significant advantages in predicting diseases, diagnosing conditions, and assisting in treatment planning. However, the use of machine learning in the medical field still faces important challenges particularly with regard to the interpretability of these models.

Traditional models like logistic regression and decision trees are relatively simple, making their predictions easier to explain. In contrast, more advanced models such as gradient boosting, random forest, and deep learning—despite their superior predictive accuracy—tend to behave like "black boxes." This lack of transparency is a major obstacle in the medical field, where clinicians and patients need to understand the rationale behind predictions for them to be accepted and trusted. The development of XAI techniques is crucial to addressing this issue. XAI aims to bridge the gap between the high performance of modern machine learning models and the need for understandable, interpretable predictions. The development of XAI tools such as SHAP, LIME, and Influence Functions allows for the use of machine learning in medicine with greater confidence. These tools not only offer transparency but also reinforce the reliability and validity of the models, helping to align predictions with established medical knowledge.

As machine learning continues to evolve, integrating these explainability techniques will be essential to ensuring its practical and ethical use in healthcare. The future of medicine may increasingly rely on machine learning, and with it, explainable models may become an indispensable tool to enhance both diagnostic accuracy and decision-making processes. Through these advances, machine learning can greatly help to improve patient care, facilitate personalized treatment strategies, and aid healthcare professionals in making informed decisions.

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Consensus

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Chinese expert consensus on sequential surgery following conversion therapy based on combination of immune checkpoint inhibitors and antiangiogenic targeted drugs for advanced hepatocellular carcinoma (2024 edition)

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SUMMARY Up to half of hepatocellular carcinoma (HCC) cases are diagnosed at an advanced stage, for which effective treatment options are lacking, resulting in a poor prognosis. Over the past few years, the combination of immune checkpoint inhibitors and anti-angiogenic targeted therapy has proven highly efficacious in treating advanced HCC, significantly extending patients' survival and providing a potential for sequential curative surgery. After sequential curative hepatectomy or liver transplantation following conversion therapy, patients can receive long-term survival benefits. In order to improve the long-term survival rate of the overall population with liver cancer and achieve the goal of a 15% increase in the overall 5-year survival rate outlined in the Healthy China 2030 blueprint, the Professional Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases of Chinese Preventive Medicine Association, Chinese Society of Liver Cancer, and the Liver Study Group of Surgery Committee of Beijing Medical Association organized in-depth discussions among relevant domestic experts in the field. These discussions focused on the latest progress since the release of the Chinese expert consensus on conversion therapy of immune checkpoint inhibitors combined antiangiogenic targeted drugs for advanced hepatocellular carcinoma (2021 Edition) and resulted in a new consensus on the modifications and supplements to related key points. This consensus aims to further guide clinical practice, standardize medical care, and promote the development of the discipline.

Keywords hepatocellular carcinoma; molecularly targeted therapy; hepatectomy; immune checkpoint inhibitors; conversion therapy

Liver cancer is a malignancy with high morbidity and mortality rates. In China, approximately 367,700 new cases of liver cancer and 316,500 liver cancer-related deaths occur annually (*1*). Hepatocellular carcinoma (HCC) is the predominant type of liver cancer, accounting for about 75.0-90.0% of all primary liver cancer cases (*2,3*). Due to the insidious onset of liver cancer, most patients present without clinical symptoms during the early stages. Consequently, 39.0% to 53.6% of patients are diagnosed with advanced HCC at their initial visit (*4*). In this consensus, the definition of advanced HCC aligns with the *Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2024 Edition)* and the Barcelona Clinic Liver Cancer (BCLC) staging system. Advanced HCC is characterized by macrovascular invasion or extrahepatic metastases detected on imaging, corresponding to CNLC stage IIIa/IIIb or BCLC stage C.

Less than 30% of patients with HCC are suitable candidates for radical surgery at the time of initial diagnosis. Currently, effective curative treatments for advanced HCC remain limited, and the prognosis is generally poor (*5*). According to current guidelines, the treatment for advanced HCC is typically non-surgical, as radical surgery aimed at achieving a cure is rarely feasible. For patients with CNLC stage IIIa HCC, and especially those with tumor thrombi in the main trunk of the portal vein, transcatheter arterial chemoembolization (TACE) or TACE combined with systemic therapy is recommended as the preferred treatment option. Surgical resection may only be considered in very rare cases following a multidisciplinary team (MDT) discussion. For patients with CNLC stage IIIb HCC (with extrahepatic metastases), systemic therapy and local therapy are recommended as first-line treatment options (*3*). The European Association for the Study of the Liver (EASL) guidelines and the BCLC staging system recommend systemic therapy as the sole treatment option for patients with BCLC stage C HCC (*5,6*). With advances in systemic antitumor therapies, combination regimens involving immune checkpoint inhibitors (ICIs) and antiangiogenic targeted drugs (AATDs) have demonstrated remarkable efficacy. Current guidelines have prioritized the use of ICIs combined with AATDs as the first-line treatment for advanced HCC (*3,7,8*) . This shift in treatment paradigms not only offers improved survival benefits from systemic antitumor therapy but also opens up new possibilities for down-staging, conversion therapy, and sequential surgical interventions in patients with advanced HCC (*9*).

Since the publication of the *Chinese Expert Consensus on Conversion Therapy of Immune Checkpoint Inhibitors Combined with Antiangiogenic Targeted Drugs for Advanced Hepatocellular Carcinoma (2021 Edition)*, four consensuses on the topic of conversion therapy have been released in China (*10-13*). To further advance the concept of sequential surgeries following conversion therapy, improve clinical practice, enhance the long-term survival rates of patients with advanced HCC, and promote progress in the field, the Professional Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases of Chinese Preventive Medicine Association, the Chinese Society of Liver Cancer, and the Liver Study Group of the Surgery Committee of Beijing Medical Association organized in-depth discussions among domestic experts in the field. Through comprehensive

analysis of clinical outcomes and extensive discussion of the key points of the consensus, this updated consensus has been reached.

Applicable population

This consensus applies to patients diagnosed with advanced HCC. Intended users include clinicians, nurses, technicians, as well as personnel involved in teaching and scientific research related to the diagnosis and treatment of HCC at medical facilities of all levels.

Search strategy

The consensus was reached by lead experts through searches of the databases PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang, as well as reviews of abstracts from recent international conferences, including those of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). The search terms included "hepatocellular carcinoma," "molecularly targeted therapy," "ICI," "immunotherapy," " conversion therapy," "transarterial intervention therapy," "systemic therapy," "local therapy," and "radiotherapy." Both subject terms and free-text terms were combined to perform searches in both Chinese and English.

Description of recommendations

This consensus has been registered on the International Practice Guideline Registration for Transparency (PREPARE) Platform (registration number: PREPARE-2024CN846). During updating of the consensus, the lead expert group made preliminary revisions based on published data and clinical experience. Consensus opinions and supporting evidence were thoroughly discussed through consultations online, in writing, and offline. Feedback was incorporated into updates, followed by an expert seminar where the final draft was voted upon. Each consensus opinion was adopted with an agreement rate of 80% or more among the attending experts. The consensus applies the Oxford Centre for Evidence-Based Medicine Grading (2011 edition) to evaluate evidence levels (graded as 1~5). Recommendations are categorized as: Strong recommendation (Recommendation A); Moderate recommendation (Recommendation B); or Weak recommendation (Recommendation C) (*3*).

Consensus Text

1. Current treatment landscape for advanced HCC and the necessity of conversion therapy

For patients with advanced unresectable HCC, traditional systemic therapies and local treatments, including transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), transarterial radioembolization, stereotactic body radiation therapy (SBRT), and ablation, as well as combination regimens involving these approaches, are commonly utilized treatment options (*3*).

Previous studies have shown that SBRT for primary lesions of advanced HCC can achieve an objective response rate (ORR) of up to 81.5%, with a median progression-free survival (PFS) of 4.0-6.0 months and a median overall survival (OS) of 8.0-15.4 months. The 1-, 3-, and 5-year survival rates were 36.2-56.0%, 12.4-28.0%, and 4.3-20.0%, respectively (*14,15*). TACE is the recommended treatment for patients with CNLC stage IIIa HCC and is also an optional treatment for some patients with CNLC stage IIIb HCC who may benefit from TACE in controlling intrahepatic tumor growth (*3,16*). Depending on disease severity and treatment variations, the ORR of TACE ranges from 3.9-37.9%, the median PFS is 3.6-6.3 months, and the median OS is 5.0-15.5 months. The 1-, 3-, and 5-year survival rates are 36.0-68.0%, 13.0-22.0%, and 5.0-8.0%, respectively (*17-22*). Compared to TACE, HAIC offers several advantages, including a lower incidence of adverse reactions, broader indications, and minimal impact on subsequent surgery, leading to its increased use in clinical practice over the past few years (*23*). For patients with unresectable large HCC, studies have found that HAIC achieves a better ORR than traditional TACE (*24,25*). Significant progress has also been made in the combined use of various non-surgical local treatments, including TACE combined with radiotherapy (*26,27*), TACE combined with ablation (*28,29*), and TACE combined with HAIC (*30*). These have been found to control local lesions in some patients with advanced HCC for which the treatment is indicated, thereby improving survival outcomes (*16*).

Over the past few years, ICIs and AATDs have achieved encouraging results in the treatment of various solid tumors. Drugs such as sorafenib, lenvatinib, donafenib, bevacizumab, pembrolizumab and atezolizumab have been confirmed to be effective in the treatment of advanced HCC (*31-34*). Theoretically, ICIs and AATDs can have a synergistic effect by improving the immune microenvironment and by also promoting the normalization of immune-active cell functions. Based on a large phase III randomized controlled clinical trial, ICIs combined with AATDs - as exemplified by atezolizumab plus bevacizumab, sintilimab plus a bevacizumab biosimilar, camrelizumab plus apatinib and pembrolizumab plus lenvatinib - have displayed considerable clinical efficacy in the treatment of advanced unresectable HCC: The ORR is as high as 21-30%, and the median OS is 19.2-22.1 months (*31,35-37*). In studies involving patients with unresectable HCC, subgroup analysis showed that the median OS has

not yet been reached (95% CI, 13.5-unreached), with a median PFS of 5.7 months (95% CI, 4.2-8.3) for Chinese patients treated with atezolizumab in combination with bevacizumab (*38*). Different ICI combinations, such as durvalumab plus tislelizumab and nivolumab plus ipilimumab, also yielded positive results, with an ORR of 20.1-36% and median OS of 16.4-23.7 months (*39,40*). Based on the survival benefits of the combination regimens, the immunotherapy based regimen, and especially the more widely used combination of an ICI and an AATD, has become the preferred first-line treatment for advanced HCC (*3,8*).

In addition, the exploration of local therapy plus systemic therapy in the treatment of advanced HCC is also actively being promoted. For example, the phase III EMERALD-1 study suggested that, compared to a placebo plus TACE, durvalumab plus bevacizumab plus TACE significantly prolonged PFS and increased the ORR in patients with unresectable HCC (*41*). However, the OS benefit still requires further follow-up for clarification. Several phase II clinical studies and real-world retrospective studies have explored local treatments such as TACE or HAIC combined with tyrosine kinase inhibitors (TKIs) (*42,43*), ICIs (*44*), or ICIs plus TKIs regimens (*45-50*). Those studies have shown that, according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), the ORR can reach 41-67.9%; according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), the ORR ranged from 54.1% to 83.3%, the median PFS ranged from 9 to 15 months, and the median OS ranged from 16.3 to 23.9 months, demonstrating stronger tumor shrinkage and survival benefits compared to either local therapy alone or systemic drug therapy alone. However, high-level evidence from randomized controlled trials is still lacking to further confirm its long-term efficacy and safety (*13*).

Systemic therapy, and especially ICIs combined with AATDs therapy based on high-level research evidence, has changed the treatment landscape for advanced HCC to a great extent. However, drug resistance and disease progression remain challenges that patients with advanced HCC have to face. The underlying reason for the poor overall prognosis in these patients is that neither single nonsurgical local therapies nor systemic therapies, nor a combination thereof, are radical treatments, and thus they provide limited oncological benefit. Conversion therapy for HCC refers to the use of systemic therapy, local therapy, or a multi-dimensional/multi-modal combination of both, to convert an advanced, unresectable tumor into one that is resectable, thereby providing patients with the opportunity to undergo sequential radical surgery to remove heterogeneous lesions, reduce tumor recurrence, and prolong patient survival. With advances in comprehensive treatment, the combination of ICIs plus AATDs conversion therapy and sequential surgeries for advanced HCC has, to some extent, overcome the efficacy bottleneck, leading to improved long-term survival. As novel therapies emerge, sequential surgeries will become possible for patients with advanced HCC following successful conversion therapy using ICIs plus AATDs. A point worth noting is that conversion therapy and existing systemic therapy or local therapy are not incongruous. The key difference is that conversion therapy is the first step in the whole treatment process and successful conversion may provide patients with the opportunity for sequential surgery, which can result in greater survival benefits. Even if conversion therapy fails, patients can still receive standardized and reasonable therapies.

Consensus 1

Conversion therapy for advanced HCC has two goals: (1) surgical resectability and (2) oncological benefits (Evidence Level 2, Recommendation A).

Consensus 2

The ICI and AATD-based conversion therapy and the current systemic therapy or local therapy are not incongruous. Even if conversion therapy fails, patients can receive standardized and reasonable treatment. Therefore, the treatment paradigm of sequential surgery following conversion therapy based on a combination of ICI and AATD is recommended (Evidence Level 1, Recommendation A).

2. Current status of conversion therapy for advanced HCC

A study reviewing and analyzing clinical data on 835 patients with liver cancer suggested that patients with advanced HCC and hepatic macrovascular invasion or extrahepatic metastasis mainly received local treatment, systemic treatment, supportive treatment, or surgery; less than 10% of those patients underwent surgery, and the overall prognosis remained poor (*51*). Previous studies have indicated that in patients with advanced HCC who underwent liver resection, the median recurrence-free survival (RFS) after surgery is only 1.5-10.0 months, the 1- and 3-year RFS rates were 13.3-66.0% and 0.6-15.0%, respectively, and the median OS was 4.8-19.5 months, with 1- and 3-year survival rates of 28.6-50.0% and 12.5-22.7%, respectively. The 5-year survival rate was only 4.0-23.8%, which are still significantly lower than the survival rates associated with radical treatment (*17,52-57*).

Most advanced HCCs are not resectable. Even when direct surgical resection is performed, there are still problems such as rapid postoperative recurrence and high recurrence rates. Several studies have confirmed that advanced tumor stages are risk factors for early recurrence and poor prognosis after surgery in patients

with HCC (*53,58,59*). Based on considerations such as improving surgical resectability and oncological benefits and in light of the current status of systemic treatment for HCC, patients with advanced HCC are the key population for conversion therapy. Although there is still a lack of evidence from head-to-head randomized controlled studies, previous studies have suggested that immuno-targeted conversion therapy plus sequential surgeries can offer tumor-free survival and OS benefits for patients with advanced HCC and that surgical resection after conversion is an independent prognostic factor for achieving a longer OS in patients with initially unresectable HCC (*60-62*).

In addition, mounting evidence shows that the survival outcomes of patients with HCC who have been successfully down-staged to meet transplantation criteria are similar to those of patients who were initially eligible for transplantation. If, for example, liver transplantation is performed after patients with HCC who initially did not meet the Milan criteria are down-staged with TACE, radiofrequency ablation, radiotherapy or radioembolization, those patients could achieve similar survival benefits as those who initially met the Milan criteria and received a liver transplant. The 1-, 3-, and 5-year survival rates of the patients were 91.4% *vs.* 92.0%, 82.8% *vs.* 85.7%, and 70.4% *vs.* 74.1% (p = 0.540), respectively. The 1-, 3-, and 5-year relapse-free survival rates were 87.9% *vs.* 87.5%, 75.9% *vs.* 81.3%, 63.8% *vs.* 66.1% (p = 0.667), respectively*(63)*. If patients with HCC who did not meet the UCSF (University of California, San Francisco) criteria are first down-staged to meet the UCSF criteria before liver transplantation, they can receive similar survival benefits as those who initially met the UCSF criteria and who received a direct liver transplant (*64*).

Consensus 3

Conversion therapy is mainly used to treat advanced HCC, which corresponds to CNLC stage IIIa and IIIb or BCLC stage C. Radical surgery or liver transplantation after conversion therapy may result in long survival benefits (Evidence level 2, Recommendation A).

2.1. Single-agent ICI, AATD or local conversional therapy

From individual cases and empirical conversion based on local treatment to systemic conversion based on immuno-targeted therapies, the exploration of conversion therapy for liver cancer has accelerated. The ORR for first-line single-agent ICI and first-line single-agent AATD therapy are 14.3-17% (*40,65,66*) and 2-18.8% (*34,67-69*), respectively, in advanced unresectable HCC. When monotherapy is used, the insufficient objective response and limited tumor shrinkage have restricted its use in conversion therapy (*70-72*).

Local therapy is more effective in directly targeting and controlling tumor lesions, with a higher ORR and successful conversion rate compared to targeted or immune therapy alone (*73*). A meta-analysis showed that patients with initially unresectable HCC treated with TACE alone had an overall ORR of 44% and an overall successful conversion rate of 10% (*74*). In one retrospective study, HAIC for advanced HCC had an ORR of 34.9% and a conversion rate of 29.7% (*75*). The median RFS for concurrent chemoradiotherapy combined with HAIC yielded a conversion rate of 16.9%, a median OS of 23.0 months, and a 5-year OS of 49.6% (*76*). For HCC patients with main hepatic vascular invasion, radical resection following concurrent chemoradiotherapy combined with HAIC returned a successful conversion rate of 26.5%. The survival benefit of those patients was better than that of patients undergoing direct hepatectomy, with median RFS time of 32.0 months *vs.* 3.0 months (p = 0.002) and 1-, 3-, and 5-year RFS of 57.7% *vs.* 16.7%, 38.5% *vs.* 11.1%, and 11.5% *vs.* 5.6%, respectively (p = 0.004). The 1-, 3-, and 5-year relapse-free survival rates were 57.7% *vs.* 16.7%, 38.5% *vs.* 11.1%, and 11.5% *vs.* 5.6%, respectively (p = 0.004) (*77*). The conversion rate for patients with initially unresectable HCC receiving TACE combined with HAIC reached 48.8%, which was higher than that for TACE alone, and PFS was superior to TACE alone, too. However, there were no significant differences in OS (*30*). In general, compared to that of targeted monotherapy (*e.g.*, sorafenib and lenvatinib), local therapy as exemplified by TACE and HAIC has more potential of successful conversion, but its clinical efficacy is still not satisfactory.

2.2. ICI plus AATD conversion therapy

As the ICI combined AATD regimen has become the preferred treatment recommendation for advanced unresectable HCC, combined regimens have gradually become the mainstream approach in the exploration of conversion therapy.

At present, immuno-targeted conversion therapy for advanced HCC is mostly examined in small samples or retrospective clinical studies. The patients studied are mainly BCLC stage C, with an ORR of 23.3-53.1% and a successful conversion rate of 15.9-55.4% (*61,62,78-81*). Professor Shichun Lu reported the results of a study of 100 patients with HCC and portal vein tumor thrombosis who underwent surgery (*82*). Of these, 36 patients underwent immuno-targeted conversion therapy and sequential surgery, while 64 patients underwent direct surgery. The median follow-up was 27.9 months. Propensity score matching indicated that the 2-year cumulative survival rate was 73.3% *vs.* 38.2% in patients receiving sequential surgery following conversion therapy and in patients receiving surgery directly, while

the 2-year relapse-free survival rate was 47.9% *vs.* 16.7%. The risk of postoperative recurrence was reduced by 76% (HR: 0.24, 95% CI: 0.123 to 0.467, $p < 0.001$) and the risk of death was reduced by 77% (HR: 0.23, 95% CI: 0.121 to 0.638, $p = 0.003$).

In a Phase II clinical study, 56 patients with advanced HCC and large vessel tumor thrombosis received treatment with lenvatinib plus a programmed death-1 (PD-1) inhibitor. According to mRECIST and RECIST 1.1 assessments, the ORR was 53.6% and 44.6%, respectively. According to imaging evaluation, the successful conversion rate was 55.4%. Surgical resection was performed in 21 cases (37.5%) after conversion. The median PFS of 56 patients with advanced HCC was 8.9 months, the 1-year PFS rate was 46.2%, the median OS was 23.9 months, and the 1-year survival rate was 72.8%. Multivariate Cox regression analysis indicated that successful conversion was an independent protective factor for both PFS (HR: 0.29, 95% CI: 0.15-0.57, $p < 0.001$) and OS (HR: 0.31, 95% CI: 0.15-0.66, $p = 0.002$) (*61*).

Another study reported the long-term efficacy of immuno-targeted conversion therapy and sequential radical resection in 100 patients with initially unresectable HCC, who underwent 3 to 28 cycles of immuno-targeted conversion therapy (*83*). The 1-, 3-, and 5-year cumulative survival rates were 98.0%, 83.1%, and 74.5%, respectively. The 1-, 2- and 3 -year recurrence-free survival rates were 67.5%, 54.8% and 49.6%, respectively. Both rates were significantly better than the 5-year survival rate of a historical survival data at the same stage and were not inferior to the 5-year survival rate of a cohort with a historical data of early-stage liver cancer who underwent surgical resection (60%) (*57*).

Therapies such as HAIC and TACE are invasive procedures that are performed during hospitalization. In contrast, the administration of ICIs combined with AATDs is more convenient, as it can be done in a day-care ward or even at home. The incidence of severe adverse events is low, and most adverse reactions can be managed with drug cessation or simple supportive treatment, leading to recovery. Notably, the relatively high ORR of ICIs combined with AATDs may improve the conversion rate for advanced HCC, enabling more patients to undergo potentially curative surgery.

Consensus 4

ICIs plus AATDs is the recommended approach for conversion therapy for advanced HCC. Specific regimens include atezolizumab plus bevacizumab, camrelizumab plus apatinib, sintilimab plus bevacizumab biosimilar, and pembrolizumab plus lenvatinib. The combination regimen with a higher ORR may have a higher potential for successful conversion of advanced HCC, and hence is more recommended (Evidence level 2, Recommendation B).

Consensus 5

For patients with advanced HCC undergoing ICI plus AATD conversion therapy, the following criteria must be met: (1) Child-Pugh class A liver function; (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1; (3) 18-75 years of age; (4) Expected survival time longer than 3 months; (5) No history of gastrointestinal hemorrhage within the past 6 months; For patients who do not meet the above criteria, exploratory treatment may still be considered based on the individual situation (Evidence level 2, Recommendation B).

Considering the onset time of combined immunotherapy, risk of progression, and patient compliance and based on the interval of post-treatment evaluation in phase III clinical studies, treatment response should be evaluated every 3 cycles (6-8 weeks after the start of treatment) of combination therapy (*36*). Depending on changes in the patient's condition, the evaluation interval can be shortened or extended as appropriate.

Clinical studies have reported that, for unresectable HCC, the median time to response assessed by mRECIST was 2.7 months (range 1.2 to 11.8) for pembrolizumab plus lenvatinib and 1.9 months (range 1.1 to 9.2) for camrelizumab plus apatinib (*84*). Hence, although the median response time for immuno-targeted therapy for unresectable HCC is 2 to 3 months, some patients may require a longer period to respond. In clinical research and practice of conversion therapy, there have also been cases of successful conversion after nearly one year of treatment. As reported by Professor Tianqiang Song, the conversion time was 2 to 15 months, and the median conversion time was 4 months (*85*). In the Phase II prospective clinical study conducted by Professor Shichun Lu, the median time from the start of conversion therapy to surgery was 109 days (ranging from 77 to 219 days), with successful conversion occurring in most patients within 5 cycles of immuno-targeted therapy (*61*). Given that immuno-targeted therapy has become the standard treatment for advanced HCC, the extension of the evaluation window will not affect patients' ability to accept reasonable treatment. Therefore, the evaluation window can be appropriately extended for patients for whom surgery is not indicated so that they have more opportunity to undergo radical surgery.

Consensus 6

The response to conversion therapy should be evaluated once every three cycles of conversion therapy, and the intervals may be adjusted based on the patient's condition. Appropriate extension of the evaluation window may increase the chances

of performing a radical resection to some extent (Evidence level 2, Recommendation B).

2.3. Value of synergistic local treatment based on ICIs plus AATDs

Local treatment may have a synergistic effect with systemic treatment. Using TACE as an example, AATDs can inhibit neovascularization in HCC treated with TACE, thus further enhancing the therapeutic effects of TACE. After TACE treatment, the expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1) increases, weakening the immune response; ICIs can block CTLA-4 and PD-1, thereby restoring the anti-tumor action of the immune system (*86,87*).

Some studies have reported that the successful conversion rate of ICIs plus AATDs combined with local therapy in patients with initially unresectable HCC is 22-60%, though the long-term survival outcomes still need to be confirmed by extended follow-up (*88-90*). Due to the lack of head-to-head comparative studies and differences in patient characteristics, definitions of conversion success, and resectability criteria across various studies on conversion, whether immuno-targeted therapy combined with local treatment can improve long-term survival benefits while increasing the likelihood of conversion still needs to be further validated.

In addition to efficacy, safety and pharmacoeconomics are also important factors affecting the selection of conversion therapy. Based on clinical practice, an increase in treatment intensity inevitably increases the risk of treatment-related adverse events. Local and systemic therapies each have specific contraindications. For example, TACE should be used with caution in patients with HCC and main portal vein or left and right branch tumor thrombus. Due to blocked portal blood flow into the liver, TACE may aggravate liver ischemia and lead to liver failure. Additionally, combining drug therapy with local treatment makes it more complicated to identify the drug efficacy. Therefore, when deciding on conversion therapy, efficacy and safety should be balanced in accordance with the actual circumstances of patients to ensure their quality of life, reduce their medical burden, and increase the objectivity of efficacy evaluation. According to clinical studies, about 70% of patients who were successfully converted used immuno-targeted therapy without additional local therapy (*62,83*). Considering factors such as efficacy and safety, a progressive combined conversion strategy can be adopted, that is, the ICI and AATD therapy is the first-line conversion regimen, used to identify patients sensitive to immuno-targeted therapy, who can then continue with the initial regimen alone. For some patients who respond poorly to immuno-targeted therapy (no successful conversion or exhibiting signs of disease progression), local treatment should be added to intensify therapy, promote tumor antigen release, enhance anti-tumor immunity, and improve the speed and success rate of conversion therapy (*91*).

Consensus 7

Immune-targeted therapy is the basis of the treatment paradigm of sequential surgery following conversion therapy. For patients who have a poor response to immune-targeted therapy (Progressive Disease or Stable Disease), adding local treatment under the guidance of a multidisciplinary team may help accelerate the conversion process and increase the conversion rate. (evidence level 2, recommendation B).

3. Key issues with conversion therapy involving ICIs combined with AATDs

Various studies on sequential surgery for advanced HCC have gradually been compiled, and clinical efficacy has significantly improved. The immuno-targeted conversion therapy and sequential surgery model in particular has evolved from early case-based exploration into a systematic approach to conversion, with significant improvements in conversion efficiency, and that model may become the mainstream paradigm for radical treatment of advanced liver cancer. However, several clinical issues with the immuno-targeted conversion therapy and sequential surgery model still need to be addressed, including the determination of surgical indications for conversion therapy, the optimal timing of surgery, key procedures and perioperative management after conversion therapy, as well as the evaluation of prognosis and management of follow-up after conversion therapy.

3.1. Value of and indications for sequential surgeries following immuno-targeted conversion therapy

No prospective, head-to-head randomized controlled studies have compared the continuation of the initial systemic or local treatment after successful conversion and sequential surgeries. Therefore, more high-level evidence is needed to ascertain the value of sequential surgeries following conversion therapy.

One study involving patients with initially unresectable HCC who had a radiological or clinical complete response after conversion therapy suggested that the 3-year cumulative survival (88.1% *vs.* 87.9%, $p = 0.89$) and PFS (27.8% *vs.* 40.8%, $p = 0.34$) were comparable between the watch-and-wait group and the surgical resection group (*92*). In another study of 144 patients with initially unresectable HCC who met resection criteria after immuno-targeted therapy plus TACE therapy, patients with a partial response who underwent surgeries had a better OS and PFS than those who did not (*93*). However, the benefit of surgeries was

not observed in patients with a complete response. Some findings have also suggested that clinical complete response does not equate to pathological complete response, and residual surviving cancer cells may still lead to a high rate of recurrence, so the necessity of post-conversion surgery should be emphasized (*94,95*). At present, an increasing number of studies have confirmed the survival advantages of sequential surgeries after conversion therapy compared to continued local and/or systemic therapy. A multicenter, real-world retrospective study involving 405 patients with intermediate-to-advanced liver cancer compared the outcomes of successful conversion surgery with continued local and systemic therapy (*96*). Multivariate Cox regression analysis indicated that surgery was a predictive factor for OS but not for event-free survival. Similarly, a multicenter retrospective study of 150 patients with CNLC stage IIIb HCC found that patients who underwent surgery after successful immuno-targeted conversion therapy had a longer survival than those who did not (*97*). Surgery was identified as an independent predictive factor for survival (HR = 0.195, 95% CI: 0.061-0.626, $p = 0.006$), but there were no significant differences in PFS between the two groups. In a study of 101 patients with unresectable HCC by Professor Huichuan Sun, median follow-up was 21.5 months. Multivariate Cox regression analysis indicated that liver resection after conversion was an independent predictive factor for patient survival (HR = 0.050, 95% CI: 0.007-0.365, $p = 0.003$) (*60*).

In addition, surgical intervention reduces the long-term use of drugs, lowering the risk of adverse drug reactions and drug resistance. Pathological examination of surgically excised specimens helps to evaluate the efficacy of conversion therapy and assess patient prognosis, thereby guiding postoperative adjuvant treatment. Therefore, growing evidence from real-world and Phase II clinical studies on conversion, along with breakthroughs in long-term patient survival, has increasingly revealed the value of surgery in conversion therapy.

Consensus 8

Considerations for surgical resection after conversion therapy:

(1) Radical tumor resection is the key for disease cure; (2) Surgical intervention may shorten the time of ICIs and AATDs use to a certain degree, thereby reducing drug resistance and drug-related adverse reactions; (3) Pathological examination of the tumor helps to confirm the effectiveness of conversion therapy and guide the subsequent adjuvant therapy (Evidence level 2, Recommendation A).

Sequential surgeries should not be considered for patients with disease progression following conversion therapy. Radical surgery may be indicated when patients are down-staged to CNLC stage I or BCLC stage A after conversion therapy. When selecting radical resection, the patient must also meet the general surgical criteria for technically resectable surgery (*93*), including Child-Pugh class A or B liver function and adequate residual liver volume. Due to the presence of background liver disease and the potential for liver tissue damage caused by ICIs and AATDs, the standard residual liver volume after surgery can be moderately increased to ≥ 35% of the standard liver volume for non-cirrhotic patients and ≥ 45% for cirrhotic patients. The 15-min retention rate of indocyanine green (IOG) should be < 20%. The hepatic vascular inflow and outflow tract should be intact and blood flow should be satisfactory after surgery. The structure of the biliary tract should be intact and drainage should not be obstructed. The ECOG-PS score should be 0-1, and the American Society of Anesthesiologists (ASA) rating should be no higher than III.

When the liver tumor is converted a technically unresectable to a technically resectable state, that is, the above general surgical criteria have been met, and the benefits by imaging evaluation have been obtained after the conversion treatment (such as a partial response according to mRECIST). Then, if no further response by imaging evaluation can be obtained after two or more consecutive evaluation cycles, and the tumor thrombus or extrahepatic metastatic lesions can be resected simultaneously, surgical resection or superimposed local treatment (including ablation, intervention, radiotherapy, *etc.*) can also be considered, even if the tumor has not yet been down-staged to CNLC stage I or BCLC stage A. In cases of liver decompensation, liver transplantation may be an option (*98*). Complete resection of the tumor may eliminate the potential impact of tumor heterogeneity on prognosis, however, tumor debulking surgery is not recommended.

Consensus 9

For advanced HCC with downstaging and/or potentially resectable tumors after conversion therapy, radical surgery is recommended. The following technical criteria must be met for sequential radical resection after conversion therapy: (1) Child-Pugh class A or B liver function; (2) Adequate future liver remnant; (3) ICG 15-min retention rate < 20%; (4) Preservation of adequate vascular and biliary inflow/outflow after surgery; (5) The bile duct structure is intact with unobstructed drainage postoperatively; (6) ECOG-PS score of 0-1; (7) ASA classification no higher than grade III. (Evidence level 2, Recommendation B).

Consensus 10

Conversion therapy is considered successful and radical resection can be performed when patients with BCLC stage C HCC and extrahepatic metastases meet

the following conditions: the extrahepatic lesions are no longer active according to imaging, or the reduced and/or inactive extrahepatic lesions are deemed resectable (Evidence level 3, Recommendation B).

3.2. Response to conversion therapy and related evaluations

3.2.1. Evaluation of general status and routine laboratory results

Evaluation of general status includes changes in clinical symptoms, mental state, physical condition, appetite, and weight, which can be assessed *via* models such as ESOG-PS score. Routine laboratory results include the complete blood count, liver and kidney function tests, and coagulation profiles.

3.2.2. Imaging evaluation

Tumor response is evaluated using contrast-enhanced imaging (enhanced MRI or CT), with reference primarily to RECIST 1.1, mRECIST, and the Liver Imaging Reporting and Data System (LI-RADS) 2018 Edition developed by the American College of Radiology. RECIST 1.1 uses changes in tumor diameter as the basis for evaluating treatment response, while mRECIST evaluates changes in tumor enhancement during the arterial phase. mRECIST and LI-RADS have similar criteria for assessing the treatment response in HCC.

Lesion necrosis is the basis for the gradual absorption and disappearance of tumors after treatment. Necrosis occurs first, while lesion absorption and disappearance proceed more slowly. Yu *et al.* (*99*) systematically reviewed 23 studies (n = 2,574) on molecularly targeted therapies for HCC. According to mRECIST, patients with an effective treatment response had a significantly better OS than those without such a response. However, RECIST 1.1 failed to indicate significant differences in OS between responders and non-responders. Similarly, Jung *et al.* (*100*) reported that in patients with advanced HCC who received TACE plus radiotherapy, those with an effective treatment response according to mRECIST had a significantly better OS than did those without such a response. After tumor necrosis, significant histological and biological changes occur, meaning that necrotic lesions should no longer be considered for tumor staging or prognosis. Therefore, mRECIST is more appropriate for imaging evaluation of the response to conversion therapy.

Arizumi *et al.* (*101*) reported that patients with advanced HCC treated with sorafenib had a significantly higher median OS when their tumors decreased or completely disappeared in arterial phase enhancement compared to patients with no change in enhancement (19.9 months *vs.* 6.0 months, $p < 0.001$). This suggests that decreased arterial phase enhancement could serve as an early indicator of treatment effectiveness. In clinical practice, decreased or absent arterial phase enhancement appears earlier than a reduction in tumor size or tumor disappearance, so arterial phase enhancement is a suitable imaging marker for assessing the treatment response in advanced HCC. It helps determine the optimal timing for radical surgery while reducing adverse effects and drug resistance from prolonged local or systemic therapy.

Among the imaging techniques commonly used in diagnosing HCC, MRI offers unique advantages by providing non-invasive data such as diffusion-weighted imaging (DWI). DWI-based diffusion restriction features have been widely used in the qualitative diagnosis of primary tumors and tumor thrombi (*102,103*). During DWI, water molecule diffusion in active tumor lesions is restricted, resulting in lower apparent diffusion coefficient (ADC). After successful treatment and tumor necrosis, water molecule diffusion is restored, leading to increased ADCs (*104,105*). In a study by Lu *et al.* (*106*), after 6 months of radiofrequency ablation in patients with HCC, the ADC value of necrotic tumor lesions increased from 1.2×10^{-3} mm²/s before treatment to 1.5×10^{-3} mm²/s six months after treatment.

^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (18F-FDG PET-CT) can be used to evaluate the treatment response of extrahepatic metastases. The primary criterion for determining tumor necrosis is the absence of increased contrast agent uptake (*107*).

A study involving 20 patients with advanced HCC treated with PD-1 inhibitors and lenvatinib found that the tumor-to-normal liver standardized uptake value ratio (TLR) was correlated with the pathological treatment response (*108*). Another study of 28 patients with advanced HCC receiving immuno-targeted conversion therapy found that the maximum standardized uptake value and TLR changes were more pronounced in the major pathological response group than in the non-major pathological response group (*109*). TLR changes demonstrated a strong predictive value for a major pathological response.

Consensus 11

The mRECIST criteria are more suitable for the radiologic assessment of the response of advanced HCC to conversion therapy. Contrast-enhanced MRI offers advantages in radiologic assessment. The complete disappearance of arterial phase enhancement and the absence of restricted diffusion can serve as imaging features with which to evaluate complete necrosis of tumor lesions after conversion therapy. The complete disappearance of arterial phase enhancement is considered to be a decisive feature. 18F-FDG PET-CT is another choice for assessment of the treatment response of extrahepatic metastases (Evidence level 2, Recommendation B).

3.2.3. Evaluation of tumor-related blood markers

In addition to imaging studies, changes in blood tumor markers are important indicators with which to evaluate the objective response to conversion therapy. Shao *et al.* (*110*) reported that in patients with advanced HCC receiving ICI monotherapy, early responders in terms of serum alpha-fetoprotein (AFP) levels (defined as a > 20% reduction in serum AFP within 4 weeks of starting treatment) had a significantly higher ORR compared to early non-responders (73% *vs.* 14%, $p < 0.001$). Moreover, early responders had a longer median OS (28.0 months *vs.* 11.2 months, $p = 0.048$) and median PFS (15.2 months *vs.* 2.7 months, $p = 0.002$). Normalization of AFP levels following immuno-targeted therapy has been associated with improved survival, while patients with post-treatment AFP levels > 20 μg/L face an increased risk of postoperative recurrence (*111*). In a retrospective study of patients with advanced HCC treated with a combination of TKI and PD-1 inhibitors, imaging assessment according to mRECIST and a decrease in AFP to the normal range predicted a pathological complete response, with a sensitivity of 91.7%, a specificity of 84.6%, and an overall prediction accuracy of 88.0% (*112*). Sun *et al.* (*113*) found that after 6 weeks of PD-1 inhibitor treatment, a reduction of > 50% in abnormal protein induced by vitamin K absence/antagonist-II (PIVKA-II) and AFP was associated with a higher ORR, as well as a longer PFS and OS. Additionally, a retrospective study of patients with advanced HCC treated with nivolumab monotherapy found that patients with a partial or complete response had a significantly lower neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) after treatment compared to those with stable or progressive disease (*114*).

Other tumor liquid biopsy markers, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), cell-free DNA (cfDNA), and soluble programmed death-ligand 1 (sPD-L1), have shown potential in predicting the efficacy of immuno-targeted therapy. However, the current lack of large-scale clinical trial data corroborating these markers means that their clinical use needs to be studied further.

Consensus 12

For patients with pre-treatment positive serum alpha-fetoprotein (AFP) and PIVKA-II, a significant decrease in AFP and/or PIVKA-II levels often suggests an effective response to conversion therapy. Reduction and long-term maintenance of normal levels of AFP and/or PIVKA-II may indicate complete necrosis of the tumor tissue (Evidence level 3, Recommendation B).

3.3. Key points of surgical resection and perioperative complications after conversion therapy

The functional liver volume after conversion therapy for advanced HCC can be accurately measured using radiological techniques. The percentage of functional liver volume with respect to standard liver volume can also be calculated. In addition, digital imaging software is now available for 3D reconstruction of the liver, which can help with an accurate preoperative measurement of functional liver volume and the facilitation of reasonable surgical planning (*115,116*).

Consensus 13

Changes in the functional liver volume after conversion therapy can be assessed with a radiological examination. Surgical procedures can be planned based on 3D image reconstruction. (Evidence level 2, Recommendation A).

The key technical features of surgical resection after conversion therapy include resection of a large volume of the liver, a negative resection margin and adequate future liver remnant, resection of macrovascular tumor thrombi in the preserved liver, reconstruction of hepatic vessels and biliary tracts in the preserved liver, and simultaneous resection of extrahepatic metastases. Since surgical procedures are relatively complex, they should be performed at qualified facilities.

Some studies have shown that sequential resection after conversion therapy is more challenging than direct resection. There are potential complications such as increased blood loss, longer operating time, and more postoperative complications. However, accurate preoperative assessment can ensure the safety of the surgery (*117*). In a prospective cohort study by Professor Shichun Lu, 100 patients who underwent surgery after conversion therapy had no uncontrolled Grade 3 or higher drug-related adverse events before surgery, and R0 resection was achieved in all of them. Despite requiring procedures such as large-volume liver resection, a high rate of portal vein reconstruction, and extensive lymph node dissection, no patients experienced Clavien-Dindo Grade IIIb or higher complications postoperatively. Moreover, these surgeries did not increase the risk of perioperative mortality (*61,62,83,118*). Although surgery after conversion therapy for advanced HCC is more complex, it remains generally safe and feasible.

Consensus 14

Surgery can be safely performed after advanced HCC is down-staged. However, Surgical difficulty may increase and should be performed at experienced facilities (Evidence Level 3, Recommendation B).

3.4. Postoperative pathological evaluation

There is mounting evidence regarding the correlation between preoperative and postoperative imaging, the

pathological response to treatment, and prognosis. The prognostic value of a pathological response to treatment has also been reported. Studies have found that achieving a pathological complete response (pCR) to systemic therapy is associated with an improved RFS in patients with advanced HCC (*60*). For HCC, however, the threshold value for predicting survival and stratifying prognosis based on the ratio of viable tumor cells (RVTCs) remains to be established. Based on pathological evaluations of HCC specimens from patients who underwent conversion therapy and sequential surgery, Professor Shichun Lu's team found that patients with a pCR had a better RFS and OS compared to those without a complete response. When 15% was used as the optimal threshold for RVTCs to predict prognosis using receiver operating characteristic (ROC) curve analysis, patients with an RVTCs ≤ 15% had a better RFS and OS compared to those with an RVTCs > 15%. Thus, RVTCs can serve as a reference for prognostic evaluation and an aid in postoperative adjuvant treatment decision-making (*119*).

Accurate pathological evaluation must be based on standardized specimen collection. Tumor specimens often have extensive necrosis and regional viable tumor cells, so the surgical team should mark the superior and inferior poles of the tumor specimen after resection using surgical sutures or other methods. The anatomical relationship of the tumor specimen and areas where viable tumor cells are likely to be found should be indicated as much as possible, and these markings should be noted on the pathology request form for the pathologist's reference. For patients who undergo thrombectomy or lymph node dissection, the removed tumor thrombi should be marked and submitted with the superior and inferior poles clearly identified. The tumor can be dissected along the thrombus path for marking, and lymph node specimens should be numbered and submitted for inspection. All visible satellite nodules and tumor thrombi should be evaluated during pathological sampling. For specimen fixation and collection, relevant guidelines should be followed (*3,119*).

Consensus 15

Pathological examination of the excised specimen is an important indicator of the efficacy of immuno-targeted conversion therapy and patient prognosis. A higher level of remission may suggest a better prognosis and can also guide postoperative adjuvant treatment. To improve accuracy, attention should be paid to the standardization of specimen collection, labeling, and submission for examination (Evidence Level 3, Recommendation B).

3.5. Perioperative pharmacological treatment

There is currently no consensus on whether ICIs and AATDs should be discontinued prior to hepatectomy (*120,121*). ICIs may induce immune-related inflammation in the liver, potentially increasing liver fragility. AATDs may increase the risk of bleeding during hepatectomy and impair tissue repair, leading to delayed healing of surgical wounds and incisions. To ensure surgical safety, the timing of AATD discontinuation should be determined based on the drug's half-life. For example, the half-life of lenvatinib is 28 hours, the half-life of sorafenib is 25-48 hours, and the half-life of bevacizumab is 18-20 days. Therefore, the advisable approach is to stop the TKI 3-7 days before surgery and to discontinue bevacizumab 4-6 weeks prior to the procedure. There is currently no evidence suggesting that the timing of ICI discontinuation is related to surgical safety, and ICI discontinuation can be synchronized with the cessation of AATD.

Mounting evidence has indicated that Immunotherapy based combination regimens are promising options for postoperative adjuvant therapy in patients with HCC (*122-125*). However, standardized treatment protocols for systemic adjuvant therapy have yet to be established. A phase III clinical trial (IMbrave 050) evaluated the efficacy and safety of adjuvant treatment with atezolizumab plus bevacizumab versus active surveillance in patients with HCC who were at high risk for recurrence after surgical resection or ablation (*122,126*). Results indicated that the combination regimen reduced the risk of recurrence by 28% but did not indicate a benefit in OS, with grade 3-4 treatment-related adverse events occurring at a rate of 34.9% in the combination regimen group. Professor Shuqin Cheng evaluated the efficacy and safety of sintilimab monotherapy as an adjuvant treatment for patients with HCC and microvascular invasion. They reported that sintilimab monotherapy significantly improved RFS compared to active surveillance, with a median RFS of 27.7 months versus 15.5 months. However, the benefit in OS needs to be verified with a longer follow-up. The incidence of grade 3-4 treatment-related adverse events in the sintilimab group was 12.4% (*123*). A prospective multicenter cohort study investigated the efficacy of immunotherapy or immunotherapy combined with other adjuvant treatments versus no adjuvant treatment in patients with HCC who were at high risk for recurrence (*124*). Results indicated that immunotherapy or immunotherapy combined with other adjuvant treatments could prolong RFS. Additionally, several studies have noted the preliminary efficacy of immunotherapy alone or in combination with targeted therapy as adjuvant treatment. Phase III clinical trials, such as KEYNOTE-937 (NCT03867084), CheckMate 9DX (NCT03383458), JUPITER 04 (NCT03859128), and EMERALD-2 (NCT03847428), to evaluate these strategies are still ongoing.

For patients who have successfully undergone conversion immunotherapy followed by sequential

surgery, conversion therapy has been shown to be effective. Given that the current standards for postoperative adjuvant therapy have not been fully established, part or all of the original treatment regimen is generally adopted in clinical practice for postoperative adjuvant therapy to treat patients who have undergone conversion therapy followed by surgical resection (*10,12*). Professor Shichun Lu initiated systemic adjuvant therapy 1 month after surgery based on pathological findings from resected samples following conversion therapy. The key points of this strategy are as follows: If a pathological examination reveals no residual viable tumor cells in the resected specimen, indicating a complete pathological response, the original ICI treatment is continued for 6 months. If residual viable tumor cells are ≤ 50%, indicating a partial pathological response, the original ICI treatment is continued in combination with an AATD for 6-12 months. If > 50% of residual viable tumor cells are present, or if the pathological examination detects new lesions that were not seen on imaging, indicating no response to treatment, the treatment regimen should be adjusted based on pathological and genetic findings. A study involving 47 patients with initially unresectable HCC who underwent immuno-targeted therapy and sequential resection followed by adjuvant therapy found that, after treatment, these patients met the criteria for discontinuing adjuvant therapy and remained free of recurrence thereafter, with a median follow-up of 32 months. The cumulative survival rates at 1 and 3 years were 97.7% and 90.7%, respectively, while the RFS rates 1 and 3 years after surgery were 91.0% and 71.3%, respectively, with a median RFS of 40 months. During postoperative adjuvant therapy, no grade 3 or higher adverse events were reported, although 9 patients discontinued therapy because of adverse events (*127*). Moreover, for patients with advanced HCC who have undergone successful conversion therapy followed by sequential resection, adopting an adjuvant treatment strategy based on results of a postoperative pathological examination may lead to postoperative recurrence rates comparable to those of patients with a low rate of recurrence undergoing primary curative resection.

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TKIs should be discontinued 3-7 days before hepatectomy and bevacizumab should be discontinued 4-6 weeks before surgery, while ICIs may be discontinued concurrently with AATDs. ICIs alone or ICIs plus AATDs should be continued for 6-12 months after surgery based on specific postoperative pathology results (Evidence Level 3, Recommendation C).

3.6. Management of adverse reactions

Adverse reactions are assessed based on the patient's subjective descriptions, along with indicators such as electrocardiograms, chest X-rays, thyroid function tests, blood tests, myocardial enzymes, urinalysis, and liver function tests. Common adverse reactions related to immunotherapy mainly include the following: (1) Skin: Rash, mucositis; (2) Cardiovascular: Hypertension, immune myocarditis; (3) Gastrointestinal: Nausea, vomiting, diarrhea, colitis; (4) Endocrine: Thyroiditis, hypothyroidism, hyperthyroidism; (5) Pulmonary: Immune pneumonitis; (6) Renal: Renal insufficiency; and (7) Liver: Elevated transaminases, liver dysfunction (*128,129*).

Monitoring liver transaminase and bilirubin levels is important. When transaminase levels rise to less than 3 times the upper limit of normal (ULN), ICI treatment can continue. When transaminases increase to 3-5 times the ULN (excluding 5 times the ULN), ICI treatment may continue based on individual circumstances, in conjunction with prednisone therapy at a dose of 0.5-1.0 $mg \cdot kg^{-1} \cdot d^{-1}$. If transaminase levels rise to 5-20 times the ULN (excluding 20 times the ULN), ICI treatment may continue based on individual circumstances, while prednisone therapy should be increased to 1-2 $mg \cdot kg^{-1} \cdot d^{-1}$. If transaminase levels exceed 20 times the ULN, ICI treatment should be permanently discontinued, and prednisone therapy at 1-2 $mg \cdot kg^{-1} \cdot d^{-1}$ may be administered.

Special attention should be paid to cases where both transaminase and bilirubin levels are elevated. When bilirubin increases to 1-2 times the ULN, ICI treatment may continue based on individual circumstances, in conjunction with prednisone therapy at 1-2 $mg \cdot kg^{-1} \cdot d^{-1}$. If bilirubin increases to 3-4 times the ULN, ICI treatment should be permanently discontinued, and prednisone therapy at 1-2 $mg \cdot kg^{-1} \cdot d^{-1}$ should be administered. If necessary, other immunosuppressive agents may be used.

Due to differences in their target mechanisms and inhibition profiles, AATDs may cause different adverse reactions. Common adverse events associated with TKIs include hypertension, diarrhea, hand-foot syndrome, fatigue, anorexia, rash, proteinuria, liver dysfunction, and hypothyroidism. Unlike liver adverse reactions related to immunotherapy, liver damage caused by TKIs tends to resolve relatively readily with a reduced dose or discontinuation and symptomatic treatment. Common adverse reactions to monoclonal AATDs such as bevacizumab include hypertension, fatigue, diarrhea, or abdominal pain. These are more likely to cause severe bleeding compared to TKIs and ICIs, so the bleeding risk should be assessed and monitored more closely during clinical use (*130,131*).

Previous data showed that, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, the ICI plus TKI regimen had an incidence of treatment-related adverse reactions of 89.3%, with 42.9% of these being grade 3 or higher (*61*). There are

4 main levels of the management of severe adverse reactions during immuno-targeted conversion therapy: dose adjustment, discontinuation of the drug, permanent cessation of the drug, and cessation of all drugs and local treatment. Combining different drugs and local therapies may lead to overlapping adverse reactions, increasing the likelihood of treatment discontinuation. During immuno-targeted conversion therapy, regular and timely assessments need to be performed, management needs to be stringent, and patients need to complete the prescribed treatment regimen while minimizing the risk of severe treatment-related complications or death. In most cases, adverse reactions can be effectively alleviated or managed with symptomatic treatment if they are properly prevented. Specific management principles for adverse reactions can be found in the NCCN Guidelines for Management of Immune-related Toxicities and the relevant domestic consensus (*129,132*).

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Most adverse reactions associated with immuno-targeted conversion therapy are controllable and they resolve spontaneously or only require symptomatic treatment. The treatment principles for adverse reactions are as per the NCCN or domestic clinical practice guidelines for management of immunotherapy-related toxicities (Evidence Level 2, Recommendation B).

3.7. Collaboration by and the value of multidisciplinary teams in conversion therapy

Unlike simple systemic or local treatments, conversion therapy for HCC includes a wider range of therapeutic approaches and involves multiple disciplines, requiring more multidisciplinary team collaboration. Advanced HCC remains a highly heterogeneous cancer, with differences in tumor biological characteristics between individuals. Additionally, factors such as the patient's general condition, risk factors, etiology, tumor burden, and comorbidities individually affect treatment decisions. Key factors contributing to the long-term survival benefits of conversion therapy include the effective tumor shrinkage and embolization achieved by combination therapy, long-term survival benefits from immunotherapy, the thoroughness of surgical resection, and a standardized chronic disease management model

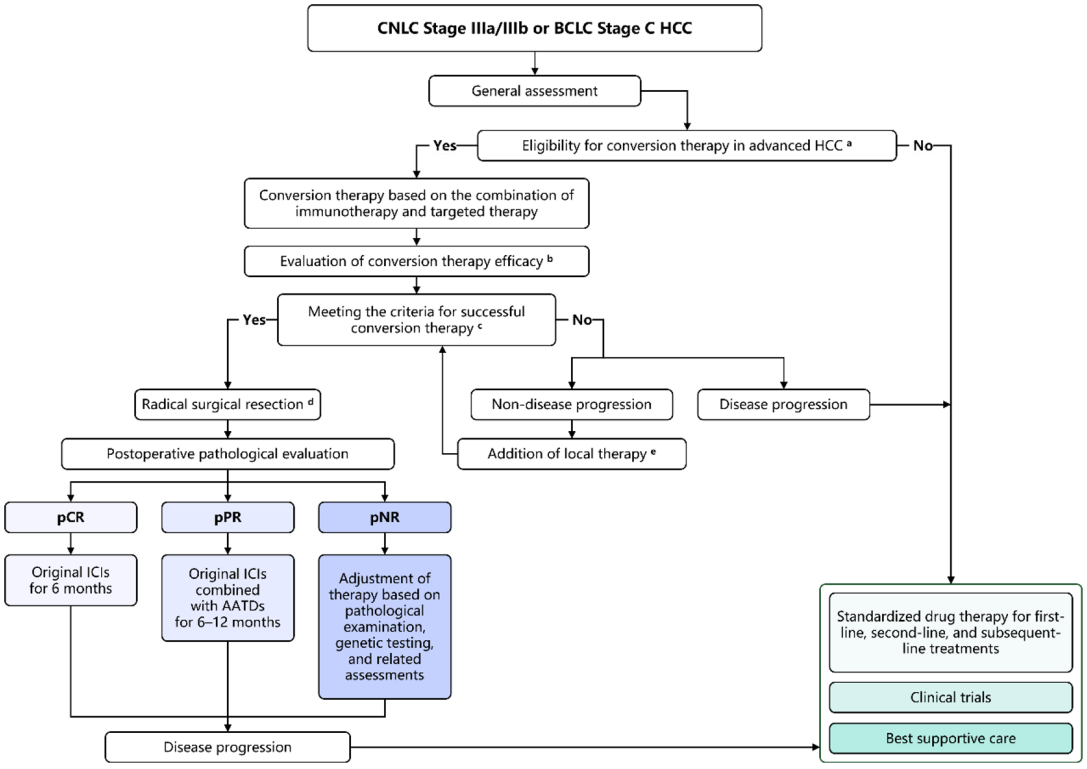

Figure 1. Sequential surgery following Immuno-targeted conversion therapy for advanced HCC. CNLC: China Liver Cancer Staging system. BCLC: Barcelona Clinic Liver Cancer staging system. pCR: Pathological complete response (no residual viable tumor cells in the resected specimen). pPR: Pathological partial response (≤ 50% residual viable tumor cells in the resected specimen). pNR: Pathological no response (> 50% residual viable tumor cells or new lesions identified in pathology). **a:** eligibility criteria for conversion therapy using immune checkpoint inhibitors (ICI) combined with antiangiogenic targeted drugs for advanced HCC. **b:** every 3 cycles of the immuno-targeted conversion therapy should be followed by an evaluation of the treatment response. The evaluation interval can be adjusted based on disease progression or the patient's condition. **c:** successful conversion criteria as downstaging and/or achieving technical resectability after conversion therapy. **d:** liver transplantation should be considered for patients with decompensated liver function. **e:** during initial and subsequent efficacy evaluations (based on modified RECIST criteria), if tumor shrinkage is < 30% or tumor growth is < 20%, local therapies may be added under the guidance of a multidisciplinary team (MDT).

following multidisciplinary team collaboration (*131*). Multidisciplinary team collaboration should occur throughout the entire process of conversion therapy, including formulation of a treatment plan, evaluation of surgical indications and the timing of surgery, management of adverse events, monitoring of treatment response, and long-term follow-up (Figure 1).

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Decisions on conversion therapy regimens, evaluation of response, the timing of surgery, and postoperative adjuvant therapy for advanced HCC should follow a standardized, individualized, and comprehensive management approach based on multidisciplinary team collaboration (Evidence Level 3, Recommendation B).

4. Prospects for the future

China has a large population of patients with advanced HCC who have complex disease, limited effective treatment options, and a poor prognosis. Improving therapeutic outcomes for advanced HCC remains a critical challenge and aligns with the focus of the Healthy China 2030 plan to reduce mortality from major diseases. The aggressive biological behavior of advanced HCC limits the efficacy of standalone treatments - be they local therapy, systemic therapy, or surgical intervention - hampering the achievement of a radical cure or the provision of a long-term survival benefit. The emergence of conversion therapy offers a new avenue for treatment of advanced HCC. Over the past few years in particular, ICIs combined with AATDs have displayed encouraging results. Looking ahead, capitalizing on the collective decision-making of MDTs and combining ICIs and AATDs with other appropriate local therapies to devise a comprehensive treatment strategy should significantly improve the feasibility and increase the success rate of conversion therapy. This, in turn, could allow more patients with advanced HCC to undergo radical resection and provide them with long-term survival benefits.

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Review

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Advances in systemic therapy leading to conversion surgery for advanced hepatocellular carcinoma

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SUMMARY Recently, a systemic therapy for advanced hepatocellular carcinoma (HCC) has been developed. The regimen for unresectable HCC varies and includes single or multi-tyrosine kinase inhibitors, monoclonal antibodies, immune checkpoint inhibitors, or their combinations. Treatment with these agents begins with sorafenib as the first-line drug for unresectable HCC. Subsequently, several systemic therapies, including lenvatinib, ramucirumab, cabozantinib, and regorafenib have been investigated and established. With advances in systemic therapy for unresectable HCC, the prognosis of patients with unresectable HCC has improved significantly than previously. Conversion surgery, consisting of systemic therapy and surgery, showed the possibility of improving the prognosis than systemic therapy alone. Although a combination of atezolizumab and bevacizumab is mostly used for initially unresectable HCC to conduct conversion surgery because of the high response rate and fewer adverse events compared to others, many trials are being conducted to assess their efficacy for initially unresectable HCC. However, the appropriate timing of surgery and interval between systemic therapy and surgery remain controversial. To address these issues, a multidisciplinary team can play a vital role in determining the strategies for treating unresectable HCC. This review describes previous and current trends in the treatment of HCC, with a particular focus on conversion surgery for initially unresectable HCC.

Keywords conversion therapy, liver resection, unresectable hepatocellular carcinoma, immune checkpoint inhibitor

1. Introduction

Systemic therapy has advanced hepatocellular carcinoma (HCC) (*1*). The treatment strategies for advanced HCC have remarkably changed over the past few decades (*2*). Treatments for advanced HCC vary according to guidelines. The Barcelona Clinic Liver Cancer (BCLC) staging system, which is widely used in Western countries, recommends systemic therapy for intermediate- and advanced-stage HCC (*3*). However, Asian guidelines, such as the Japanese or Chinese guidelines and guidelines of the Asian Pacific Association for the Study of the Liver, recommend surgery for selected patients with advanced HCC (*4-7*). One of the main reasons why Asian guidelines are more aggressive than Western guidelines is surgeons' consensus on surgical indications for HCC (*7*). Some studies have reported that hepatectomy for advanced HCC without systemic therapy offered five-year overall survival (OS), ranging between 20-53% (*8,9*). Hepatectomy offered better median survival time (MST) than systemic therapy (15.1 *vs*. 4.5 months) in patients with portal vein tumor thrombus (*10,11*). Hepatectomy plays an important role in the treatment of advanced HCC, particularly in the conversion from systemic therapy to resection.

Systemic therapy for HCC begins with sorafenib, a multikinase inhibitor for unresectable advanced HCC (*12,13*). Phase III trials of sorafenib and the SHARP trial (ClinicalTrials.gov number, NCT00105443) showed that the median OS was 10.7 *vs*. 7.9 months in sorafenib and placebo, respectively ($p < 0.001$) (*14*). However, the efficacy of sorafenib is not significant, with an MST of < 1 year and a tumor response rate of < 5% (*14,15*). Trials of other agents have shown no superiority or non-inferiority to sorafenib in patients with advanced HCC (*16-18*).

Approximately 10 years after the appearance of sorafenib, new treatments with multitargeted tyrosine kinase inhibitors (TKIs) have been started, with lenvatinib as the first-line treatment (*14,19*). Lenvatinib is an orally active inhibitor of multiple receptor tyrosine

kinases (*20-22*). The REFLECT trial (*ClinicalTrials.gov*, NCT01761266) compared the efficacies of sorafenib and lenvatinib in patients with unresectable advanced HCC (*20*). It revealed that lenvatinib was significantly superior to sorafenib in the progression-free survival (PFS) (median of 7.4 *vs*. 3.7 months in Lenvatinib and placebo, respectively), and that objective response rate (ORR) based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (*23*) were of 29.6 *vs*. 6.9% ($p < 0.0001$), respectively. Lenvatinib has the potential to play a key role in tumor downstaging because of its high response rate (40.6%) to mRECIST and antiangiogenic effects (*20,24,25*).

Furthermore, immune checkpoint inhibitors (ICIs), such as anti-programmed death receptor-1 (PD-1), anti-programmed death ligand (PD-L1), and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, have been adopted as treatments for HCC. The combination of atezolizumab, which is an anti-PD-L1 antibody, and bevacizumab (a monoclonal antibody against vascular endothelial growth factor) showed a better prognosis than single therapy of sorafenib alone in a phase III trial for unresectable HCC (*26*). Recently, the combination of durvalumab and tremelimumab has also been shown to result in better OS than sorafenib (*27*). The CheckMate 040 randomized clinical trial of nivolumab plus ipilimumab showed an improved OS (median, 22.2 months) and 60-month OS rate of 29% in patients with HCC previously treated with sorafenib. Many guidelines worldwide recommend these combination therapies for the treatment of advanced HCC (*3*).

Trials and studies on advanced HCC are increasingly being performed to investigate treatments with better prognosis, especially in advanced or unresectable HCC (*13,20-22,24-26,28-34*). The combination of hepatectomy and systemic therapies is a promising treatment expected to improve OS and reduce HCC recurrence.

In this review, we discuss the development of treatments for advanced HCC, including state-of-the-art treatment strategies and ongoing trials, and compare the differences in HCC treatments between Western and Eastern countries.

2. Combination therapies for advanced HCC

2.1. Atezolizumab plus bevacizumab

The IMbrave 150 study reported that a combination therapy with atezolizumab plus bevacizumab resulted in better OS than sorafenib (*31*). Patients were treated with atezolizumab plus bevacizumab and sorafenib. Overall survival rates at 12 months were 67.2% with atezolizumab plus bevacizumab and 54.6% with sorafenib, and median PFS was 6.8 *vs*. 4.3 months, respectively. Atezolizumab plus bevacizumab is now recommended as the first-line systemic therapy for patients with advanced HCC (*12*).

2.2. Durvalumab plus tremelimumab

Combination treatment with durvalumab (an anti-programmed cell death ligand-1) and tremelimumab (an anti-cytotoxic T-lymphocyte-associated antigen 4) showed promising results in a phase II trial in patients with unresectable HCC (*27*). A phase III trial, the HIMALAYA trial, was conducted to evaluate combination treatment in patients with unresectable HCC (*27,30*). Patients were assigned to receive durvalumab plus tremelimumab (STRIDE regimen), durvalumab, and sorafenib treatment. The trial revealed that median OS was 16.43 with STRIDE *vs*. 16.56 with durvalumab *vs*. 13.77 months with sorafenib. A four-year update of the HIMARAYA trial reported that a 48-month OS rate was higher with STRIDE than with sorafenib (25.2 *vs*. 15.1% , respectively) (*30*). Another study that included 44 patients treated with STRIDE for unresectable HCC reported a disease control rate of 53.3%, which was significantly better when used as a first-line therapy than when used as a second or later line (65.8 *vs*. 45.9%, respectively, $p = 0.034$) (*35*). In an Asian subgroup analysis of the HIMALAYA trial, STRIDE demonstrated that ORRs based on RECIST ver1.1. were 28.2% with STRIDE, 18.6% with durvalumab, and 9.0% with sorafenib (*36*). These results suggested that STRIDE is a promising treatment option for unresectable HCC.

2.3. Other promising therapies

Many trials and studies have investigated promising therapies for unresectable HCC. Combination therapy with novel agents, such as an anti-programmed death-1 antibody, showed a better response rate or prognosis than sorafenib. For example, camrelizumab plus revoceranib (*37*), sintilimab plus bevacizumab biosimilars (*38*), and lenvatinib plus pembrolizumab (*32*) have shown better prognoses in advanced HCC. Among these, treatment with lenvatinib plus hepatic intra-arterial infusion chemotherapy (HAIC) with cisplatin for advanced HCC showed prospective results in the LEOPARD trial (*39*). This phase II trial enrolled 36 patients with advanced HCC and evaluated 34 patients. The patients received the following treatments: lenvatinib, 12 mg/day for patients ≥ 60 kg and 8 mg/day for patients < 60 kg; HAIC with cisplatin: 65 mg/m^2, day 1, every 4-6 weeks, and a maximum of six cycles. The ORRs were 64.7% (95% confidence interval (CI): 46.5-80.3%) and 45.7% (95% CI: 28.8-63.4%) in mRECIST and RECIST ver1.1, respectively. Median PFS and OS were 6.3 and 17.2 months, respectively. According to these results, the LEOPARD-NEO trial, a multicenter phase II trial, aimed at assessing the safety and efficacy of lenvatinib plus HAIC using cisplatin for borderline resectable HCC, is now ongoing and is expected to show better results. Transarterial chemoembolisation (TACE) plus lenvatinib (LEN-TACE) is a promising treatment (*40*). The phase

II TACTICS-L trial, which included 62 patients with unresectable HCC, revealed a high response (ORR, 88.7%) and complete response rate (67.7%) based on the Response Evaluation Criteria in Cancer of the Liver as defined by the Liver Cancer Study Group of Japan (*41*). These promising therapies have the potential to change treatment strategies or provide better prognoses than those in the near future.

3. Outlines of conversion surgery

3.1. Conversion surgery versus neoadjuvant chemotherapy

Conversion therapy should be distinguished from neoadjuvant chemotherapy (*42*). There are significant differences between the neoadjuvant chemotherapy and conversion therapy. Conversion surgery is a treatment strategy that involves surgery following systemic therapy for initially unresectable or borderline resectable tumors that undergo radical resection, and is established for other solid cancers (*15,43,44*). Conversion surgery aims to downstage tumor burden in patients with initially unresectable cancer, providing better survival, reducing recurrence (*15,29,45*), and achieving complete resection. Recently, conversion surgery has been increasingly performed to provide better prognosis in patients with solid tumors (*15*).

Neoadjuvant chemotherapy is administered to patients with resectable tumors to decrease tumor size before hepatectomy (*46,47*). Generally, it aims to decrease the possibility of recurrence or increase the remnant liver volume to ensure safety after hepatectomy (*46*).

3.2. Conversion surgery for hepatocellular carcinoma

The treatment for patients with initially unresectable HCC after systemic therapy has not been established yet (*22,48*). In general, after a tumor is downstage from advanced or unresectable to an early stage (for example, the BCLC stage A or Chinese National Liver Cancer (CNLC) stage I), curative surgery is indicated (*12,49,50*). Patients with tumors that meet the criteria for technical resectability are also indicated for curative surgery or local treatment. Conversion surgery for initially unresectable HCC consists of a combination of systemic therapy and resection (*12,19,51*). In patients with advanced HCC, a combination of hepatectomy with sorafenib or lenvatinib reportedly improved OS compared with systemic therapy alone (*14,21,52*). However, the low response rate to systemic therapy contributed to a few patients undergoing conversion therapy (*15,53*). An improvement in the response rate would enable more patients to undergo conversion surgery than ever before (*53*).

3.3. Candidate selection for conversion surgery using a staging system

The BCLC staging system has been adopted globally for HCC treatment, particularly in Europe and the United States. According to the staging system, liver resection is limited to early-stage cases. In contrast, the CNLC staging system, established in 2017 and updated, proposes a more aggressive candidate for liver resection (*5*). The stages were defined as follows: Ia, single ≤ 5 cm; Ib, single > 5 cm or up to three tumors ≤ 3 cm; IIa, up to three tumors > 3 cm; IIb, ≥ 4 tumors; IIIa, tumor with vascular invasion; IIIb, tumor with metastases; IV, end stage.

During conversion therapy, tumors are classified into two groups: technically resectable and technically unresectable. Patients with technically unresectable HCC (CNLC stages Ia-IIa) and technically resectable HCC (CNLC stages IIb-IIIa) are potential candidates for conversion surgery. Moreover, patients with technically unresectable HCC (CNLC stages IIb-IIIa) initially undergo systemic therapy with or without local therapy, and resection is recommended if the tumor shrinks to a resectable condition. A previous study reported improved recurrence-free survival after hepatectomy following systemic therapy in patients with CNLC stage IIb/IIIa (*54*).

3.4. Candidate selection for conversion surgery based on resectability

Candidacy for conversion therapy is limited to patients with initially unresectable HCC, who have the possibility of being treated by surgery after systemic therapy (*55*). Several definitions of HCC resectability have been proposed. In one proposal, HCC was divided into three groups: resectable, borderline resectable, and unresectable, depending on four factors: distant metastasis, macroscopic curative resectability, indocyanine green clearance of a remnant liver, and macrovascular invasion (*56*). Another study also proposed a three-group classification, but it consisted of three similar factors (distant metastasis, macroscopic curative resection, and macrovascular invasion) and two different factors (ratio of future liver remnant to modified albumin-bilirubin score and tumor size) (*25,57*). However, there is no international consensus regarding the resectability of HCC. These situations make it difficult to discriminate conversion surgery from surgery after neoadjuvant therapy (*25,56*). Candidates for conversion therapy should be selected by a multidisciplinary team because many factors, including general condition, liver function, remnant liver volume, vascular invasion, and tumor size, should be considered to determine whether surgery is suitable (*50,58*). According to previous reports and trials, the conversion therapy rates differ, depending on the type and duration of systemic therapy (Table 1) (*47,58,59*). Conversion surgery may offer a better prognosis in patients with unresectable HCC who achieve pathological complete

Table 1. Conversion rates after treatments for initially unresectable hepatocellular carcinoma

Authors	Study design	Treatment (number)	Conversion rate
Takeyama *et al*. (*62*)	Retrospective	Sorafenib (*n* = 32)	12.5%
Shindoh *et al*. (*25*)	Retrospective	Lenvatinib (*n* = 107)	8.4%
Kudo *et al*. (*69*)	Retrospective	Atezolizumab plus Bevacizumab (*n* = 38)	31.8%
Ichida *et al*. (*22*)	Prospective	Lenvatinib (*n* = 49)	67.3%
Kaneko *et al*. (*53*)	Retrospective	Sofarenib (*n* = 292)	1.4%
Kaneko *et al*. (*53*)	Retrospective	Lenvatinib (*n* = 72)	2.7%
Peng *et al*. (*82*)	Prospective	Lenvatinib (*n* = 338)	1.8%

response (*60*). Advances in systemic therapy for HCC have promoted conversion therapy and its efficacy has been investigated worldwide.

3.5. Resectability for HCC

There are no established criteria for the oncological resectability of HCC or the concept of borderline resectable tumors in the field of pancreatic cancer. There has been an increasing demand for consensus on these criteria because conversion surgery has become common in recent years.

To precisely determine the operative indication for initially unresectable HCC after systemic therapy, it is necessary to clarify the definition of "unresectable" (*41,59*).

Generally, unresectable HCC is classified into two groups according to the cause: oncologically and technically unresectable HCC (*23,49*). Oncologically unresectable tumors indicate that treatments other than surgery are expected to provide better survival rates. Oncologically unresectable HCC has a poor prognosis, even if hepatectomy is successfully performed. Technically, tumors are unresectable owing to factors, such as their general condition, liver function, and insufficient liver remnant volume. Technically unresectable tumors extend to a large extent and cannot be completely and safely removed (41). In such cases, tumor shrinkage is due to the response to systemic therapy to safely undergo radical resection. These patients are eligible for conversion therapy. However, it is often difficult to clearly divide them because the two unresectable statuses partly overlap (*50*).

Recently, the Working Group of the Japan Liver Cancer Association and Japanese Society of Hepatobiliary-pancreatic Surgery proposed oncological resectability in HCC and classified the resectability of HCC into three grades: resectable, borderline resectable 1 (BR1), and borderline resectable 2 (BR2) (Figure 1) (*1*). These classifications were defined as follows: resectable, the status in which surgery alone may be expected to provide better OS compared with other treatments; BR1, the status in which surgical intervention may be expected as a part of multidisciplinary treatment to provide survival benefit; and BR2, the status in which the efficacy of surgery is unclear and the indication for surgery should be decided with discretion under standard multidisciplinary treatment (*1*). Additionally, BR2 is synonymous with initial unsuitability for surgery.

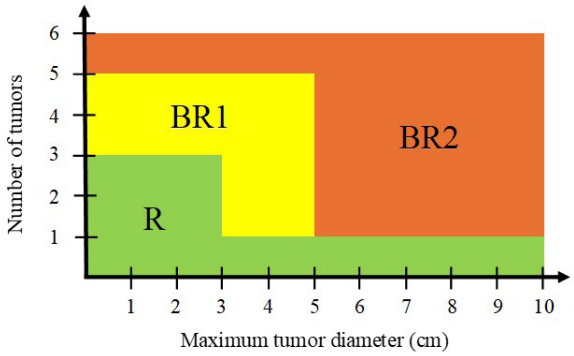

Figure 1. Resectability criteria for hepatocellular carcinoma based on the number and maximum diameter of tumors. The vertical and horizontal axes represent the number (*n*) of tumors and maximum diameter of tumors (cm), respectively. R, resectable; BR, borderline resectable 1; BR2, borderline resectable 2. Created based on the previous article (*1*).

The treatment of patients with BR2 or unresectable HCC should be carefully determined by a multidisciplinary team to offer a better prognosis.

4. Outcomes of conversion surgery

4.1. Conversion surgery with sorafenib

There have been no large cohort reports on conversion surgery after systemic sorafenib (*42*). Previous studies with a small number of patients or case reports showed that patients with initially unresectable HCC who underwent surgery after sorafenib achieved pathological response, better prognosis, and disease-free survival (*53,61,62*). However, there is no strong evidence to support sorafenib as a systemic therapy after curative conversion surgery for initially unresectable HCC. Sorafenib is not adopted as systemic therapy before conversion surgery because of its low response rate, accounting for only approximately 3% (*61,63,64*). Therefore, a few patients who have undergone conversion therapy after systemic therapy with sorafenib and have achieved a complete response can have a better prognosis (*42,61,64*). Considering these results,

conversion surgery using sorafenib is unrealistic for patients with unresectable HCC.

4.2. Conversion surgery with lenvatinib

Lenvatinib is thought to be suitable for conversion surgery because of its properties, such as suppression of tumor progression and tumor necrotic effect. A greater response rate to lenvatinib could contribute to more opportunities for conversion surgery in patients with unresectable or borderline resectable HCC. A retrospective study revealed that surgical resection after lenvetinib treatment had better disease-specific survival compared to no additional treatment after lenvatinib (hazard ratio (HR), 0.04; 95% CI, 0.01-0.30; $p = 0.002$) with a conversion surgery rate of 8.4% (*65*). In the comparison of additional treatments including surgery, ablation, TACE, and transcatheter arterial infusion chemotherapy after lenvatinib treatment, complete surgical resection showed a better prognosis than others in PFS (HR, 0.30; 95% CI, 0.16-0.58) and time-to-treatment failure (HR, 0.08; 95% CI, 0.02-0.39) (*25*). Another single-center study reported an improvement in the prognosis of patients with initially unresectable HCC after conversion surgery with lenvatinib (*66*). Successful conversion surgery with lenvatinib has been reported in some cases with survival benefits after surgery and preserved liver function, even in patients with metastases to other organs (*44,67,68*).

These results suggest that complete resection after lenvatinib treatment may offer a better prognosis than previous treatments. The prospective LENS-HCC trial was conducted to evaluate the efficacy of surgery after lenvatinib treatment in unresectable HCC (*22*). This trial revealed a high conversion rate of 67.3%. These results support conversion therapy, especially conversion surgery, after lenvatinib treatment for initially unresectable HCC.

The LENS-HCC trial is a multicenter, phase II trial performed in Japan to evaluate the efficacy and safety of preoperative lenvatinib therapy in patients with initially unresectable HCC (the Japan Registry of Clinical Trials (s031190057)) (*22*). This trial was conducted in response to the results of the phase III REFLECT trial, which showed that lenvatinib is superior to sorafenib in terms of PFS, time to progression, and ORR in patients with initially unresectable HCC (*24*). In this trial, a high response rate of 40.6% based on mRECIST for sorafenib was reported.

This trial enrolled patients with advanced HCC without a history of systemic therapy for HCC and with at least one factor suggestive of a poor prognosis as follows: macroscopic vascular invasion, extrahepatic metastasis, or multinodular tumors. The endpoint of this trial was surgical resection rate. This trial enrolled 49 patients from 11 centers in Japan. Among them, 42 patients were oncologically unresectable, and seven were technically unresectable. The patients underwent treatment with lenvatinib (12 mg/body weight/day ≥ 60 kg, or 8 mg/body weight/day < 60 kg) for eight weeks. Subsequently, resectability was evaluated by a multidisciplinary team, and the patients underwent tumor resection one or more times after the last lenvatinib administration.

The results of the trial demonstrated a high disease control rate of lenvatinib in patients with unresectable HCC, leading to a high surgical resection rate of 67.3%, and the safety and feasibility of lenvatinib therapy in conversion surgery. The trial also reported the safety and feasibility of lenvatinib because there were no cases of severe worsening of the liver functional reserve, no mortality in patients who underwent surgery, and no serious perioperative complications associated with lenvatinib administration. Although the long-term outcome remains unclear because the follow-up period was not very long (median, 9.3 months), this trial is expected to report long-term outcomes in the near future. In this trial, the patients with technically or oncologically unresectable HCC were treated with lenvatinib. However, there may be differences in the possibility of conversion surgery between the patients with technically and oncologically unresectable HCC because those with technically unresectable HCC received systemic therapy until the tumor becomes resectable, whereas those with oncologically unresectable HCC receive systemic therapy until the tumors showed a better response to systemic therapy; surgery was recommended by a multidisciplinary team from the perspective of oncology. Therefore, each patient should have a different appropriate treatment duration of systemic therapy depending on tumor conditions.

4.3. Conversion surgery with atezolizumab plus bevacizumab

Atezolizumab plus bevacizumab is widely used as the first-line treatment for advanced HCC because the IMbrave150 trial revealed the superiority of atezolizumab plus bevacizumab over sorafenib in advanced HCC (*31*). Based on the results of this trial, another study was performed to evaluate the efficacy of a combination of curative treatments after atezolizumab plus bevacizumab. In this study, 39 patients received conversion therapy. Among them, 25 achieved complete response at a rate of 35% based on RECIST ver1.1 (*69,70*). Moreover, 23% of the patients achieved a drug-free status. However, conversion therapy included liver resection, ablation, selective TACE, or their combination. The criteria for conversion surgery were unclear, and patients who did not achieve complete response underwent surgery. These conditions must be considered when results are interrupted. Seven patients underwent liver resection in this study. Other studies, including case reports, have reported complete response and better survival benefits in

Table 2. Time to progression and response according to previous reports

Authors	Treatment (number)	Assessment	Time to progression (months)	Time to response (months)
Llovet *et al*. (*14*)	Sorafenib (*n* = 299)	RECIST ver1.1	5.5 (4.1-6.9)	NA
Abou-Alfa *et al*. (*27*)	STRIDE (*n* = 393)	RECIST ver1.1	22.34	2.17 (1.84-3.98)
Abou-Alfa *et al*. (*27*)	Sorafenib (*n* = 389)	RECIST ver1.1	18.43	3.78 (1.89-8.44)
Cainap *et al*. (*16*)	Sorafenib (*n* = 521)	RECIST ver1.1	4.0 (2.8-4.2)	NA
Kudo *et al*. (*26*)	Atezolizumab plus bevacizumab (*n* = 46)	mRECIST	14.2 (10.9-16.6)	4.1 (1.3-12.3)
Kudo *et al*. (*26*)	Sorafenib (*n* = 23)	mRECIST	12.4 (4.7-NE)	4.2 (1.2-5.7)
Kudo *et al*. (*20*)	Lenvatinib (*n* = 478)	mRECIST	8.9 (7.4-9.2)	NA
Kudo *et al*. (*20*)	Sorafenib (*n* = 476)	mRECIST	3.7 (3.6-5.4)	NA
Yamashita *et al*. (*24*)	Lenvatinib (*n* = 81)	mRECIST	7.2 (5.4-9.2)	NA
Yamashita *et al*. (*24*)	Sorafenib (*n* = 87)	mRECIST	4.6 (3.5-5.4)	NA

STRIDE, Single Tremelimumab Regular Interval Durvalumab (300 mg of tremelimumab for one dose plus 1500 mg of durvalumab every four weeks); RECTST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NA, not available; NE, not estimated. The time to progression and response are shown with 95% confidence intervals.

patients with initially unresectable HCC after conversion surgery following treatment with atezolizumab plus bevacizumab (*71-76*). These results imply that liver resection after atezolizumab plus bevacizumab treatment offers a better prognosis for patients with initially unresectable HCC.

The RACB trial is an ongoing, prospective, multicenter phase II trial in Japan to evaluate the efficacy of combination therapy of atezolizumab plus bevacizumab in achieving conversion surgery in patients with unresectable HCC (the Japan Registry of Clinical Trials (s031190057)) (*45*). Inclusion criteria for this study were as follows: unresectable HCC without a history of systemic therapy, at least one target lesion based on RECIST ver. 1.1 (*70*), and a Child-Pugh score of 5 or 6. In this study, macroscopic vascular invasion, extrahepatic metastasis, and massive distribution of intrahepatic tumors were classified as unresectable HCC.

As a treatment protocol, patients diagnosed with unresectable HCC underwent systemic therapy with atezolizumab (1,200 mg/kg body weight) plus bevacizumab (15 mg/kg body weight) every three weeks. The patients were assessed radiologically using computed tomography or magnetic resonance imaging at twelve weeks after the first systemic therapy. If the tumor became resectable during the assessment, the patient received a single treatment with atezolizumab and tumor resection three weeks later. If the tumors are unresectable, the patients continue systemic therapy until they become resectable or show progression.

To assess the response of the tumors to systemic therapy, radiographic assessments were conducted every nine weeks until the tumor became resectable or progressed after the second assessment (12 weeks). The follow-up period was 18 months after inclusion.

Primary endpoint was PFS assessed by RECIST ver. 1.1 (*70*).

This study aimed to determine the efficacy of conversion surgery with atezolizumab plus bevacizumab in patients with initially unresectable HCC.

4.4. Timing of conversion surgery

The timing of surgery remains unestablished and controversial (*47,64,77,78*). Previous reports suggested that the timing of surgery should be after five cycles of ICI plus an anti-angiogenic drug (*51,79*). Other recommended patients with complete tumor remission should receive ICI treatment for six months, and patients with partial remission should receive combined treatment for 6-12 months prior to surgery (*47*). Determining the precise timing of surgery is difficult because it is not necessarily better to perform surgery as soon as possible. Early surgery can contribute to failure, whereas late surgery can lead to drug resistance and tumor progression (*53*). Time to progression and time to response have been reported for some agents, showing wide range (Table 2). The differences in time to progression and response between trials seemed to come from differences, such as patients' background, liver function, number of patients, and study design because patients' background and liver function had an influence on tolerance to systemic therapy, and the small number of patients and study design influenced data reliability. To avoid missing the ideal timing for conversion surgery, the effects on the tumor should be carefully assessed, and liver function should be preserved enough for surgery, referring to the results, such as the time to progression and time to response may be useful.

4.5. Cessation interval between systemic therapy and conversion surgery

The interval between systemic therapy and surgery should be recommended based on the half-lives of the agents used in the treatment. Patients who have undergone treatment with a TKI and bevacizumab should stop them one and 6-9 weeks before surgery, respectively (*64,80*). Wound-healing complications are well known to

be related to bevacizumab (*81*). If the cessation interval is not sufficiently long, a shorter interval may cause wound-healing complications. Patients treated with lenvatinib can safely undergo surgery one week after lenvatinib cessation (*22*). Patients who have undergone ICI treatment should stop it at the same time as anti-angiogenic drugs for > 2 weeks before surgery (*50,51*). It is not necessarily better to increase the interval between systemic therapy and surgery because of the possibility of tumor progression during the interval.

5. Conclusions

This article reviews advancements in systemic therapy for HCC and highlights the progression of a combination of surgery and systemic therapy. Prognosis has been rapidly improving since the introduction of sorafenib, and its efficacy in providing a better prognosis for unresectable HCC was revealed in a trial. Subsequently, new types of systemic therapies and novel regimens for HCC have emerged, and further investigations of their combinations have been conducted worldwide. Although systemic therapy for HCC has remarkably advanced recently, the selection of patients eligible for systemic therapy remains under investigation. The number of patients receiving systemic therapy and surgery is increasing. The timing of conversion therapy, including surgery, should be carefully determined, and the response to systemic therapy should also be evaluated with discretion. To deal with these subjects, a multidisciplinary plays an important and critical role in the treatment of HCC. Therefore further investigations are required to solve these problems.

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Original Article

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Development and validation of a machine-learning model to predict lymph node metastasis of intrahepatic cholangiocarcinoma: A retrospective cohort study

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SUMMARY Lymph node metastasis in intrahepatic cholangiocarcinoma significantly impacts overall survival, emphasizing the need for a predictive model. This study involved patients who underwent curative liver resection between different time periods. Three machine learning models were constructed with a training cohort (2010-2016) and validated with a separate cohort (2019-2023). A total of 170 patients were included in the training set and 101 in the validation cohort. The lymph node status of patients not undergoing lymph node dissection was predicted, followed by survival analysis. Among the models, the support vector machine (SVM) had the best discrimination, with an area under the curve (AUC) of 0.705 for the training set and 0.754 for the validation set, compared to the random forest (AUC: 0.780/0.693) and the logistic regression (AUC: 0.703/0.736). Kaplan-Meier analysis indicated that patients in the positive lymph node group or predicted positive group had significantly worse overall survival (OS: $p < 0.001$ for both) and disease-free survival (DFS: $p < 0.001$ for both) compared to negative groups. An online user-friendly calculator based on the SVM model has been developed for practical application.

Keywords intrahepatic cholangiocarcinoma, hepatectomy, lymph node metastasis, machine learning

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary liver cancer, accounting for approximately 10-15% of cases, with hepatocellular carcinoma (HCC) being the most prevalent (*1*). Hepatectomy is currently the primary treatment for ICC. However, only a tiny portion of patients with ICC are able to undergo surgery due to the limited availability of effective diagnostic tools (*2*). Even if surgery is undergone, a significant proportion of patients (nearly 20-50%) will suffer from relapse in the 12-24 months following surgery (*3,4*). Certain serological indicators (elevated CA19-9 or positivity for the hepatitis B virus) and pathological features (microvascular invasion (MVI), multifocal tumor, positive margins, *etc.*) are considered to be linked to the prognosis and recurrence of ICC (*5*). Of these factors, positive lymph nodes (LNs) are widely acknowledged as a substantial risk factor for both survival and recurrence. A negative correlation between the quantity of positive LNs and the overall survival rate has been noted (*6*). Hence, having information about the LN status of individuals diagnosed with ICC can yield vital insights into staging and adjuvant strategies.

There is currently a lack of consensus regarding the necessity of performing LN dissection (LND) in patients with ICC. A prominent point of contention about LND is whether it confers a survival advantage. A meta-analysis of 1,377 cases indicated that undergoing routine LND does not provide an advantage in terms of overall survival but is associated with an elevated risk of post-operative mortality (*7*). LN metastases may indicate a widespread metastatic disease rather than local dissemination, therefore diminishing the significance of LND. However, the advocates argue that the unfavorable views of LND are influenced by a bias in that LND is only performed when LN metastasis is suspected, and these patients clearly tend to have a poor prognosis. From a broader perspective, even if LND offers no benefit in terms of prognosis, it can provide precise details regarding the staging of LNs (*8*) and patients pathologically confirmed to have positive LNs should receive adjuvant treatment as soon as possible and be alert to any signs of tumor recurrence. Currently, LND is performed in less than 50% of cases (*9*), and the rate of sufficient LND (≥ 6) has plummeted to less than 20%

(*10*). Consequently, LN status cannot be determined in a large proportion of patients, hindering systematic treatment strategies following surgery. Therefore, several models to predict LN metastasis based on logistic regression, with results visually depicted in nomograms, have emerged (*11-13*). Nevertheless, the low incidence of ICC leads to a relatively limited number of cohorts, thereby restricting the number of included variables. Moreover, models developed with a small sample size are vulnerable to the influence of outliers, inevitably diminishing the accuracy and reliability of the model. Subsequently, machine learning algorithms have been implemented in medical research to address these issues. Random forest (RF), a supervised learning algorithm, creates a sizable number of decision trees and outputs predicted probability or classification by integrating the results from all generated trees (*14*). A variable is assessed and selected at each split in the decision tree, thereby maximize the disparity between the daughter nodes and recursively proceeding until the decision tree reaches maximum extension, thus effectively avoiding the problem of multicollinearity. A support vector machine (SVM) uses support vectors to identify decision surfaces (hyperplane) that maximize the classification margin between different categories (*5*). This algorithm has reduced susceptibility to outliers, hence enhancing the precision of the model.

In brief, the aim of the current study was to construct a model of the LN metastasis utilizing machine learning techniques, including clinical data and pathology information from patients in order to provide a reference for patients who have not undergone LND or who have undergone inadequate LND.

2. Patients and Methods

2.1. Patients

Data were collected on patients who underwent curative-intent hepatectomy and who were diagnosed with ICC pathologically. The data were collected from the hepato-biliary and pancreatic department of West China Hospital, SCU, between the periods of January 2010 to December 2016 and January 2019 to October 2023. Patients lacking complete pathology information, those who did not undergo curative resection, those with concurrent extrahepatic disease, or those with missing follow-up data were excluded from this study. The Ethics Committee of West China Hospital approved this study [Approval No. 2024(343)], which was conducted in accordance with the principles outlined in the Declaration of Helsinki. Due to the retrospective nature of this study, informed consent from the Institutional Review Board was waived. This study has been registered on ClinicalTrials.gov (NCT06290739).

2.2. Included variables and relevant definitions

Demographic, clinicopathological, and serological indicators included sex (male/female); age (continuous); presence of ascites (yes/no); presence of cirrhosis (yes/no); hepatitis B virus, HBV (positive/negative); platelet count, PLT (continuous); total bilirubin, TB (continuous); aspartate aminotransferase, AST (continuous); alanine aminotransferase, ALT (continuous); albumin, ALB (continuous), prothrombin time, PT (continuous); alkaline phosphatase, ALP (continuous); γ-glutamyl transferase, GGT (continuous); α-fetoprotein, AFP (continuous), carcinoembryonic antigen, CEA (negative: < 5 ng/mL, positive: ≥ 5 ng/mL); carbohydrate antigen-199, CA19-9 (< 200 U/mL, ≥ 200 U/mL); tumor number (solitary/multiple); tumor size (continuous); MVI (presence/absent); primary tumor site (right/left); tumor differentiation (poor, moderate to well-differentiated), and LN metastasis (yes/no). The presence of ascites or cirrhosis was comprehensively ascertained with preoperative imaging, intraoperative observations, and pathology. MVI and the degree of differentiation were confirmed by pathology reports. Hilar cholangiocarcinoma, a tumor originating from the caudate lobe, and bilateral lesions were excluded.

2.3. Follow-up

Patients who underwent a hepatectomy from 2010 to 2016 were followed at three-month intervals during the initial two years and then every six months thereafter until the last follow-up (January 2019). Overall survival (OS) refers to the duration between the commencement of surgery and the patient's demise due to any reason. Disease-free survival (DFS) refers to the period of time from the date of surgery until the occurrence of a relapse either within or outside the liver.

2.4. Statistical analyses and model development

Continuous data were expressed as the mean and range, and intergroup comparisons were made using either the Student's *t*-test or Mann-Whitney *U* test, depending on the circumstances. Binary variables were expressed as the frequency (proportion), and differences were tested with the χ^2 test or Fisher's exact test. This study complies with the Transparent Reporting of a multivariable prediction model for individual Prognosis or Diagnosis (TRIPOD) guideline (*15*). The cohort from 2010 to 2016 served as the training set to construct three models: logistic regression (LR), a support vector machine (SVM), and a random forest (RF). Patients who underwent LND from 2019 to 2023 served as the validation set. Least absolute shrinkage and selection operator (LASSO) regression was performed to determine variables that contributed significantly to the model. Subsequently, stepwise regression was performed to simplify the model. Without compromising the goodness of fit of the model, some adjustments to certain variables were empirically made

based on a previous review of the literature. Moreover, optimal hyperparameters for the SVM and RF were determined *via* a 5-fold cross-validation. Ultimately, the hyperparameters for the machine-learning models were as follows: SVM (*Kernel = linear, Cost* = 0.1) and RF (*mtry* = 2; ntree = 132). A receiver operating characteristics (ROC) curve was plotted for each model, and a model with an outperforming area under the curve (AUC) was selected and applied to patients who did not undergo LND. Finally, survival analysis between predicted N1 (LN metastasis) and N0 (without LN metastasis) was graphed *via* a Kaplan-Meier curve and calculated using a log-rank test. A flowchart is shown in Figure 1. The data were analyzed, models were constructed, and outcomes were plotted using the software R (version 4.2.2), (packages: "glmnet," "car," "MASS," "pROC," "survival," "survminer," "e1071," "randomForest," and "shiny").

3. Results

3.1. Patient demographics

A cohort of 271 patients with ICC who underwent LND at various time periods was included this study (Table 1). Of patients with ICC who undergo hepatectomy at this hospital, around 30-40% undergo LND. Figure 2a shows that the rate of LN biopsy was 44.5% (170/382) in the early cohort (2010-2016) and slightly lower at 34.7% (101/291) in the late cohort (2019-2023). However, the rate of adequate LN examination was higher in the later at 36.6% (versus 28.2% in the former), but not significantly so (p = 0.192) (Figure 2b). Overall, the incidence of LN metastasis among individuals who had received LND was 53.5%, with a somewhat greater proportion in the early cohort (56.5%) compared to the late cohort (48.5%), but not significantly (p = 0.253) (Figure 2c). The incidence of liver cirrhosis, the incidence of MVI, the platelet count, and ALT and GGT levels in the validation group were markedly higher than those in the training cohort. In turn, positivity for CEA, multiple lesions, poor differentiation, prothrombin time (PT), and tumor size were significantly greater in the training set.

3.2. Variable screening

The raw dataset consisted of 21 features including demographics (sex, age, ascites, HBV infection, and liver cirrhosis); serological indicators (PLT, PT, TB, ALT, AST, ALB, ALP, GGT, AFP, CEA, and CA19-9), and pathology (tumor size, tumor number, MVI, primary site of the tumor, and tumor differentiation) that needed to be simplified. To streamline the model, control multicollinearity, and remove variables that had minimal impact on the model, LASSO regression was initially performed (Figure 3a). Five-fold cross validation was performed, and the number of variables associated with the minimum value of binomial deviance was incorporated, including a total of 9 parameters: *age*, *platelet count*, *total bilirubin*, *AFP*, *CEA*, *CA19-9*, *tumor number*, *primary tumor site*, and *tumor differentiation*. (Figure 3b). A study has indicated an association between sex and LN metastasis (*16*), but there is no conclusive evidence that the remaining excluded variables are correlated with LN metastasis. The importance of CEA and CA19-9 has been emphasized in numerous studies (*9,17,12*), but other serological indicators have little value in predicting LN status. AFP is a valuable tumor marker for diagnosing HCC and predicting its prognosis, but it has limited utility with regard to ICC. The aggressiveness of a tumor can be associated with tumor size, tumor number, or tumor differentiation. Hence, some pathological features are crucial to predicting the incidence of LN metastasis. MVI is a prognostic marker of HCC recurrence and survival and

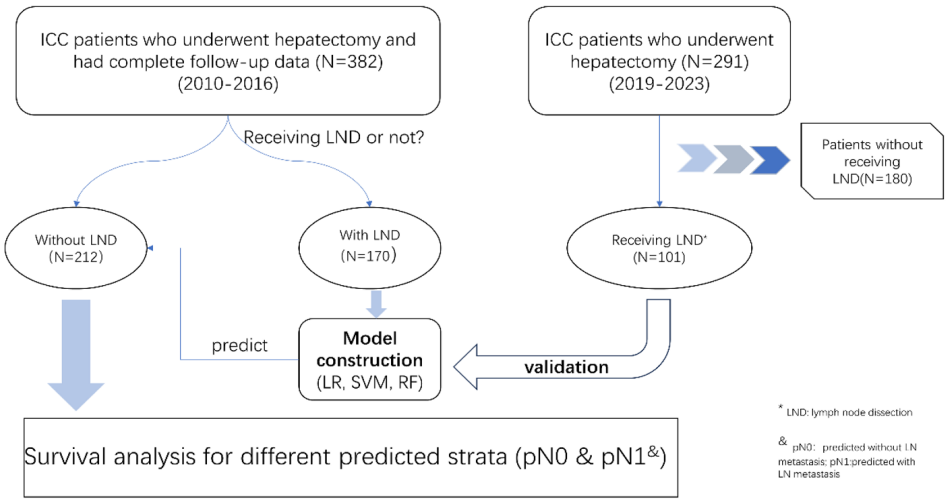

Figure 1. Flowchart for patient screening.

Table 1. Baseline patient characteristics

Cohort	Training set (2010-2016) $N = 170$	Validation set (2019-2023) $N = 101$	*P*-value
Sex (female/male)	87/83	44/57	0.277
Age* (years)	57.20 (20-81)	59.68 (36-84)	0.056
Ascites (no/yes)	142/28	80/21	0.465
HBV (no/yes)	130/40	85/16	0.175
Cirrhosis (no/yes)	158/12	74/27	< 0.001&
PLT (*10^9/L)	183.35 (70-355)	201.67 (54-450)	0.034&
PT (S)	11.62 (9.3-15)	11.13 (9-25)	0.004&
TB (μmol/L)	23.07 (3.8-544)	25.34 (4-358)	0.733
ALT (IU/L)	46.30 (4-620)	70.53 (9-912)	0.036&
AST (IU/L)	45.27 (14-831)	58.41 (15-748)	0.185
ALB (g/L)	42.13 (23.7-50)	42.18 (25-51)	0.937
ALP (IU/L)	169.15 (45-1482)	173.71 (49-979)	0.820
GGT (IU/L)	159.54 (11-1971)	248.54 (10-3928)	0.038&
AFP (ng/ml)	48.60 (0.7-4035)	22.88 (1-1210)	0.482
CEA (<5/≥5 ng/mL)	111/59	81/20	0.013&
CA19-9 (<200/≥200 U/mL)	89/81	64/37	0.101
Tumor number (solitary/multiple)	74/96	86/15	< 0.001&
Tumor size (cm)	6.64 (1-17)	5.64 (2-14)	0.002&
MVI (no/yes)	146/24	63/38	< 0.001&
Primary site of the tumor (right/left)	67/103	35/66	0.514
Tumor differentiation (poor/moderate to well-differentiated)	132/38	50/51	< 0.001&
Lymph node status (negative/positive)	74/96	52/49	0.253
TNLE# (<6/≥6)	122/48	64/37	0.192

*Continuous variables were expressed as the mean (range); #TNLE: total number of lymph nodes examined; &significant difference.

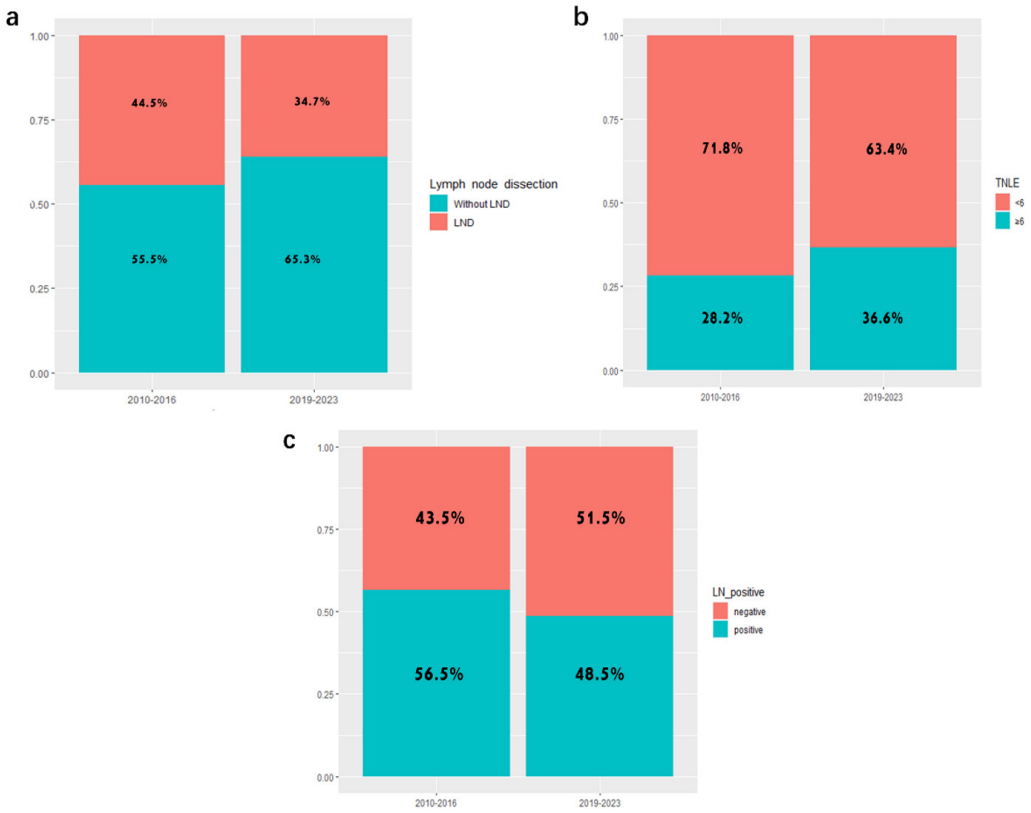

Figure 2. (a): Proportion of lymph node dissection. (b): Proportion of adequate lymph node dissection. (c): Proportion of positive lymph nodes.

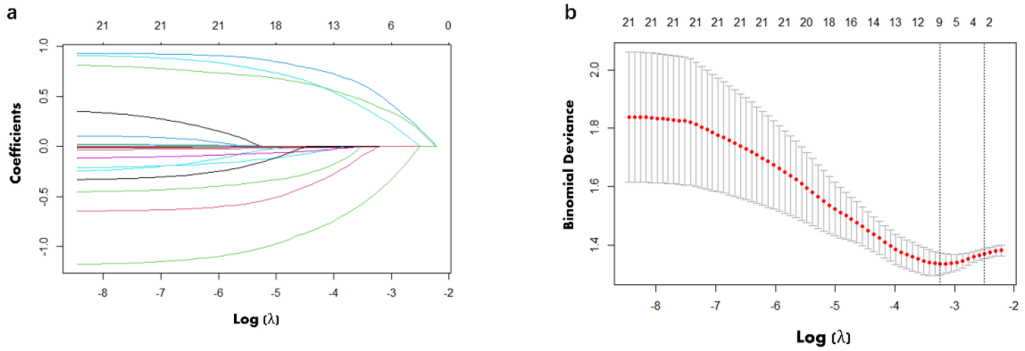

Figure 3. (a): Plots of the LASSO regression coefficients for various penalty parameters. (b): Cross validation plot of penalty terms.

Table 2. Stepwise regression outcomes

Variables									AIC*
age	PLT	TB	AFP	CEA	CA19-9	Tumor number	PST#	Tumor differentiation	221.03
-age									220.13
-age	-PLT								219.19
-age	-PLT		-AFP						218.91
-age	-PLT		-AFP				-PST		218.57

*AIC: Akaike information criterion; #PST: primary site of the tumor.

has attracted considerable attention in previous studies (*18*). Nevertheless, recent studies have provided limited findings regarding the correlation between MVI and LN metastasis. Stepwise regression of these variables was subsequently performed. Table 2 shows that a lower Akaike information criterion (AIC) corresponds to a superior model fit. Statistically speaking, the best model should include five predictors: TB, CEA, CA19-9, tumor number, and tumor differentiation. The primary site of the tumor (PST) itself has little influence on model fit, but prior studies have indicated that there is a potential link between this variable and LN metastasis (*11,17*), so the decision was to include it. Moreover, an extremely high level of TB was considered a relative contraindication for hepatectomy and there was no evidence to suggest that TB was associated with LN metastasis. As a result, it was excluded from the final model. Ultimately, the features utilized in modeling were: *CEA*, *CA19-9*, *tumor number*, *tumor differentiation*, and *PST*.

3.3. Outcomes of logistic regression

Initially, multivariate logistic regression was performed, and the results are shown in Table 3. When CA19-9 was no lower than 200 U/mL, the likelihood of LN metastasis increased significantly (HR:2.36; 95% CI: 1.17-4.84; $p = 0.017$), and this is also the case when the tumor is poorly differentiated (HR:2.56; 95% CI: 1.18-5.88; $p = 0.020$). Moreover, patients positive for CEA (HR: 2.02; 95% CI: 0.97-4.33; $p = 0.064$) or with multiple tumors (HR:1.87; 95% CI: 0.93-3.64; $p = 0.062$) tended to have LN metastasis, but the difference was not significant.

Table 3. Outcomes of logistic regression

Predictors	Hazard ratio	95% CI	*P*-value
CEA			
positive	2.02	0.97-4.33	0.064
negative	Ref.	Ref.	Ref.
CA19-9			
≥200 U/mL	2.36	1.17-4.84	0.017&
<200 U/mL	Ref.	Ref.	Ref.
Tumor number			
multiple	1.87	0.97-3.64	0.062
solitary	Ref.	Ref.	Ref.
Tumor differentiation			
poor	2.56	1.18-5.88	0.020&
moderate/well-differentiated	Ref.	Ref.	Ref.
PST#			
left	0.68	0.34-1.33	0.262
right	Ref.	Ref.	Ref.

#PST: primary site of the tumor. &significant difference.

3.4. Development and validation of three models

Out of three machine-learning models, RF had the best discrimination with the training set (AUC: 0.780; 95% CI: 0.710–0.849), followed by the LR (AUC: 0.703; 95% CI: 0.629–0.786) and SVM (AUC: 0.705; 95% CI: 0.626–0.784) (Supplemental Figure S1a, S1c, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=226,* and 4a). Figure 5 shows the importance of each variable according to the RF algorithm. The top three factors were CA19-9, CEA, and tumor differentiation. In other words, removing them would greatly affect the accuracy and heterogeneity of this model. In the validation cohort, the SVM (AUC: 0.754; 95% CI: 0.661-0.847) slightly outperformed LR (AUC:

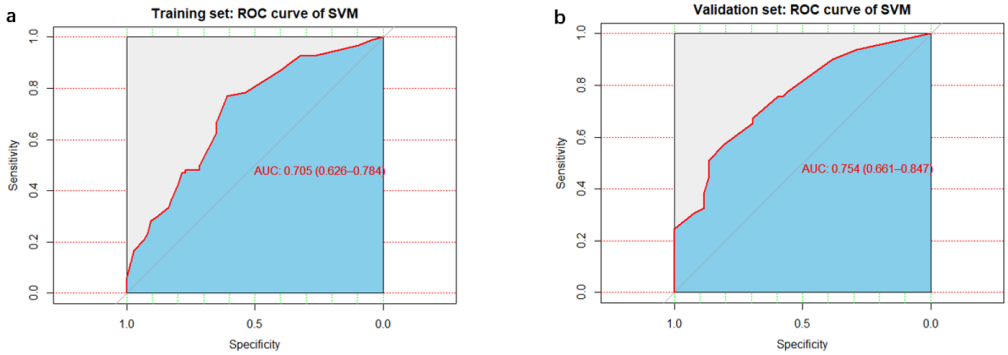

Figure 4. (a): ROC curve from the training set for the SVM. (b): ROC curve from the validation set for the SVM.

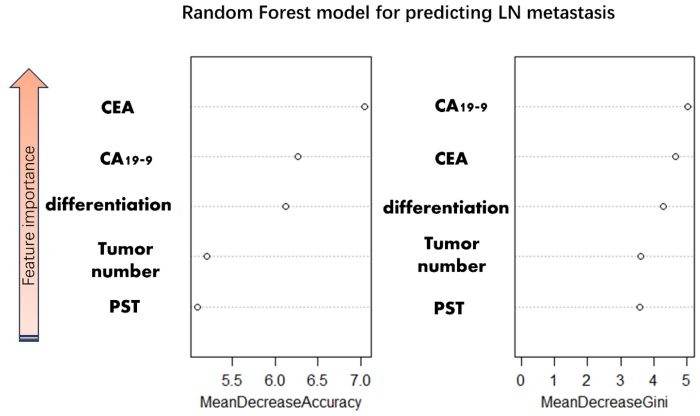

Figure 5. Feature importance in an RF model.

0.736; 95% CI: 0.640-0.833), while the RF (AUC: 0.693; 95% CI: 0.588-0.798) clearly lagged behind the other models (Supplemental Figure S1b, S1d, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=226,* and 4b). Moreover, a comprehensive assessment of the three models was performed. With the validation set, the RF model had an accuracy of 0.67 (95% CI: 0.57-0.76), with a precision (positive predictive value) of 0.86, a recall (sensitivity) of 0.39, a F1 score of 0.54, a specificity of 0.94, and a negative predictive value of 0.62. The LR model had an accuracy of 0.63 (95% CI: 0.53-0.73), a precision (positive predictive value) of 0.73, a recall (sensitivity) of 0.39, a F1 score of 0.51, a specificity of 0.86, and a negative predictive value of 0.60. The SVM model had an accuracy of 0.70 (95% CI: 0.59-0.78), a precision (positive predictive value) of 0.76, a recall (sensitivity) of 0.53, a F1 score of 0.62, a specificity of 0.84, and a negative predictive value of 0.66 (Table 4). The AUC for the RF model plummeted with the validation set, potentially indicating overfitting of the training set. In turn, the performance of the LR and SVM with the validation set was similar to that with the training set. Moreover, the SVM had the lowest misclassification rate with the validation set, followed by the RF and LR. Additionally, the SVM model had the highest F1 score (a combined measure of precision and recall), in contrast to that of the RF or LR model. After comprehensive consideration, the SVM model was chosen for the final model. To enhance the accessibility of the model, a user-friendly calculator was developed and made accessible on a website (*mieureka.shinyapps.io/Supporting_Vector_Machine_for_ICC_lymph_node_metastasis*). This calculator helps clinicians to predict the likelihood of LN metastases in individuals who did not undergo LND or who underwent an insufficient LN examination.

Table 4. Metrics of three models

Metrics	Model		
	Support Vector Machine	Logistic Regression	Random Forest
Accuracy	0.70	0.63	0.67
Specificity	0.84	0.86	0.94
Sensitivity	0.53	0.39	0.39
PPV[#]	0.76	0.73	0.86
NPV[&]	0.66	0.60	0.62
F1-score	0.62	0.51	0.54

[#]PPV: positive predictive value. [&]NPV: negative predictive value.

3.5. Survival analysis

Survival analysis was performed among patients

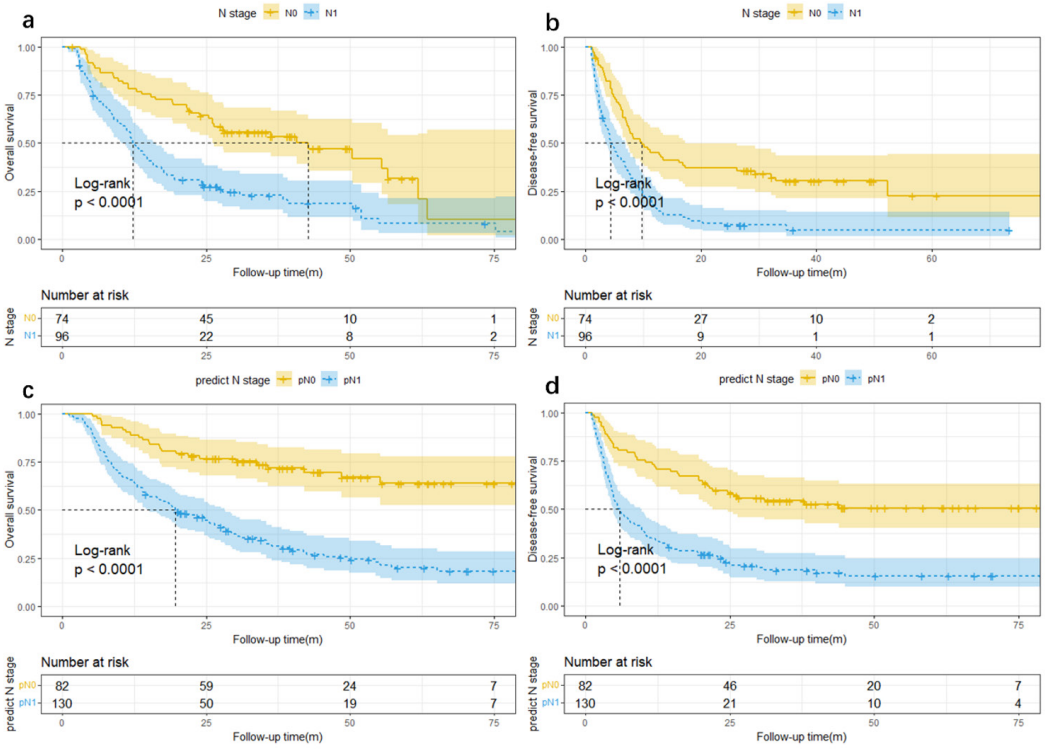

Figure 6. (a): OS curve for different N stages. (b): DFS curve for different N stages. (c): OS curve for different predicted N stages. (d): DFS curve for different predicted N stages.

undergoing LND with a different LN status and patients not undergoing LND with a different predicted LN status. The median follow-up was 17.9 months for OS and 6.5 months for DFS for individuals who underwent LND. The median OS was 12.2 months for the N1 group and 40.7 months for the N0 group, while the median DFS was 4.3 months for the N1 group and 9.5 months for the N0 group. A log-rank test indicated a significant difference ($p < 0.001$ for both), as shown in Figure 6a, 6b. Each patient who did not undergo LND was subsequently classified by the SVM into a predicted N1 group or a predicted N0 group. With a median follow-up of 25.9 months, the median OS for the pN1 group was 19.7 months. The median OS for the pN0 group was not determined at the conclusion of the follow-up (Figure 6c). The median DFS for the pN1 group was 5.7 months, with a median follow-up of 11.5 months. The median DFS for the pN0 group was not determined at the conclusion of the follow-up (Figure 6d).

4. Discussion

Presented here is the rate of LND and adequate LN examination (≥ 6) performed at our facility. Additionally, a bar plot was used to depict the rate at which LNs tested positive. LASSO and stepwise regression were performed to screen variables, eliminate multicollinearity, and streamline the final model. Three machine-learning models (LR, SVM, and RF) were subsequently established and validated with two cohorts from different time periods (2010-2016 and 2019-2023). The SVM algorithm had superior performance with both the training and validation sets, so it was therefore selected to assess the LN status in patients not undergoing LND. The Kaplan-Meier curve indicated a significant correlation between positive LNs and a poorer OS and DFS, and this trend remained in the prediction cohort, further corroborating the reliability of the current results.

LN metastasis has been confirmed to be a prognostic indicator of ICC in two large-sample studies (*6,19*). In specific terms, Zhang *et al.* found that there was a direct correlation between the number of LN metastases and the OS rate, *i.e.*, OS decreased as the number of LN metastases increased (*6*). Studies have also modified the 8th edition of the AJCC (American Joint Committee on Cancer) staging system and redefined the N stage (*20,21*). Moreover, several studies have contended that ICC with positive LNs tends to benefit from adjuvant therapy (*22,23*). A study has even reported that ICC with positive LNs can be treated with chemotherapy alone instead of surgery, without compromising prognosis (*24*). Given these findings, lymphadenectomy needs to be performed in order to acquire pathological verification of the status of LNs. Nevertheless, a substantial body of research opposes the routine performance of lymphadenectomy because it fails to confer a prognostic benefit, prolongs operating time, and increases the risks of postoperative complications (*7*) (*25-27*). Both the 8th AJCC guideline and Chinese consensus suggest routine

lymphadenectomy in patients with ICC, and the number of nodes dissected should be no less than 6. However, the rate of LND at our facility used to be less than 50% and has declined in recent years (Figure 2a). Conversely, the rate of sufficient LND has risen to nearly 40% (Figure 2b). At our facility, a mere 12.5% of patients underwent sufficient LN sampling for accurate nodal staging, which is well below the international benchmark (*28*). Hence, a system needs to be promptly developed to serve as a reference for patients with a lack of nodal staging or inadequate nodal staging.

Our model can aid in clinical decision-making both intraoperatively and postoperatively. Patients identified as having a high risk of LN metastasis should undergo LND during surgery, and the number dissected nodes and extent of LND should be ensured. For patients who underwent surgery without LND, our web-based calculator can assess the risk of LN metastasis, offering a reference for adjuvant therapy. Since a previous study has claimed that there is no statistical difference in LN metastasis between small ICC and large ICC when using a tumor size of 3 cm as the threshold (*29*), we believe that this model is applicable to surgical patients without distant metastasis. However, a point worth noting is that this model may not apply to patients with locally advanced unresectable tumors or distant metastases, as they often do not undergo LN biopsy and the risk or pattern of LN metastasis in this population has yet to be fully determined.

A point that warrants mention is that the sample sizes for the training and validation cohorts were constrained due to the low prevalence of ICC. The limited sample size may compromise the generalizability of our model, thereby hindering its application to real-world scenarios. Smaller samples might lead to potential overfitting, resulting in the model exhibiting significantly superior performance with the training set compared to the validation set. This situation also arose in the current study, where the RF model demonstrated the potential for overfitting. Moreover, having a small sample increases the likelihood of outliers, which increases the variance of logistic regression predictors and diminishes the accuracy of model predictions. We have adopted a series of strategies to address these issues. First, to ensure predictive capability, we used regularization techniques (LASSO) and stepwise regression to restrict the number of features incorporated in the model as much as possible. Second, we opted for the SVM over the RF as the final model, as a simple model is less prone to the danger of overfitting. Finally, there can be intrinsic deficiencies in developing and validating a model with the same cohort, as a group of patients may possess some unpredictable characteristics that hinder generalizability to a new dataset. Hence, we selected two cohorts from different timeframes for modeling and validation to enhance the scientific rigor of this study.

To date, a series of studies have constructed models to predict LN metastasis but with a limited sample size. Owing to the relative low incidence of ICC, most training sets consist of approximately 100 cases(*13,30,31*). This may increase the influence of outliers in logistic regression, perhaps resulting in an increase in the mean square error (MSE). Moreover, a rule of thumb for logistic or Cox regression is that 10 or 20 events per predictor (EPV) are generally considered robust and reliable (*32*), suggesting that the aforementioned studies should have 3 to 5 variables or even fewer. Machine learning is suited to solving small-sample models because it screens variables and is less impacted by outliers. In 2022, an RF algorithm was introduced to predict LN metastasis, and the machine-learning model markedly outperformed logistic regression (*12*). Surprisingly, an RF model was not constructed or validated in a cohort of patients not undergoing LND. Thus, we validated our model with a group of 212 patients not undergoing LND, and we incorporated the model in an online calculator to enhance its credibility and user-friendliness.

To the extent know, the current work describes the first online calculator based on machine learning to evaluate LN metastasis. The training set, validation, set and non-LND dataset have relatively substantial sample sizes. Nevertheless, there are several limitations worth mentioning. First, at least six LNs needed to be examined in the patients in this study in order to reduce the risk of underestimation. However, this is impossible to achieve in the real world since the rate of adequate LND is relatively low, which may be because dissection offers no prognostic benefit but potentially prolongs operating time and can results in complications (*33*). This should be considered in the design of prospective trials. Additionally, there are some discrepancies in the demographics of training and test data that might potentially compromise the sensitivity or specificity of the model when applied to the validation set. Finally, whether pN1 patients are more likely to benefit from adjuvant therapy compared to the pN0 group is still unclear, and this should be the focus of a subsequent study.

5. Conclusion

To summarize, a model to predict LN metastasis based on a SVM was developed and verified in different time cohorts for patients with ICC. The predicted outcome indicated a survival difference in patients not undergoing LND, suggesting that it is applicable to patients not undergoing LND or patients with inadequate LND. A RF model indicated that CEA, CA19-9, and tumor differentiation represented the top three crucial features, warranting particular attention. In order to enhance the accuracy and reliability of the model, multicenter studies should be conducted with large cohorts and sufficient LN sampling.

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Original Article

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Machine learning-based prognostic prediction and surgical guidance for intrahepatic cholangiocarcinoma

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SUMMARY The prognosis following radical surgery for intrahepatic cholangiocarcinoma (ICC) is poor, and optimal follow-up strategies remain unclear, with ongoing debates regarding anatomic resection (AR) versus non-anatomic resection (NAR). This study included 680 patients from five hospitals, comparing a combination of eight feature screening methods and 11 machine learning algorithms to predict prognosis and construct integrated models. These models were assessed using nested cross-validation and various datasets, benchmarked against TNM stage and performance status. Evaluation metrics such as area under the curve (AUC) were applied. Prognostic models incorporating screened features showed superior performance compared to unselected models, with AR emerging as a key variable. Treatment recommendation models for surgical approaches, including DeepSurv, neural network multitask logistic regression (N-MTLR), and Kernel support vector machine (SVM), indicated that N-MTLR's recommendations were associated with survival benefits. Additionally, some patients identified as suitable for NAR were within groups previously considered for AR. In conclusion, three robust clinical models were developed to predict ICC prognosis and optimize surgical decisions, improving patient outcomes and supporting shared decision-making for patients and surgeons.

Keywords intrahepatic cholangiocarcinoma, individualized treatment, machine learning, prediction tool, shared decision-making

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) ranks as the second most prevalent primary liver cancer, following hepatocellular carcinoma (HCC). For individuals with resectable ICC, the prognosis post-resection is discouraging, with a 5-year survival rate of only 25-35%. Notably, tumor recurrence accounts for the majority of deaths, contributing to 60-70% of cases (*1-3*). Consequently, precise prognostic assessment is of significant importance to guide personalized treatment strategies and improve the overall prognosis for ICC patients. The majority of clinical investigations concerning ICC rely on radiomic features to predict prognosis. However, it is a challenge to acquire radiomic features, and determining the region of interest (ROI) introduces subjectivity. As a result, these models are inherently intricate and hard to interpret (*4,5*). Consequently, these factors pose significant obstacles to the practical clinical application of such models.

Despite significant research advancements such as chemotherapy, targeted therapy, and immunotherapy, which have provided valuable scientific and clinical insights into the treatment of ICC (*6-8*), surgical resection remains the main potentially curative treatment. In the case of HCC, there has been frequent discussion about the difference in long-term prognosis between anatomic resection (AR) and non-anatomic resection (NAR) (*9-11*). However, in the context of ICC, the advantages of AR versus NAR remain uncertain (*12-14*). It is worth noting that the number of patients with ICC combined with cholelithiasis is higher in Eastern countries compared with that in Western countries, and the specific surgical approach in such cases remains undetermined (*15*). In conventional clinical studies, conclusions are often drawn at the population level, but

these conclusions may not necessarily benefit patients in real-world scenarios (*16*).

Artificial intelligence, particularly machine learning, exhibits undeniable advantages in addressing these issues. Machine learning has the capacity to enhance population-level evidence and facilitate the development of personalized treatment strategies for patients. However, only a few studies have compared various machine learning methods to construct high-performance predictive models for predicting recurrence and survival rates in ICC patients following radical surgery. Furthermore, there is a notable gap in the literature concerning personalized predictions for selecting surgical approaches in cases of ICC.

In the present study, multiple machine learning algorithms, dimensionality reduction algorithms, and integrated learning methods were employed to investigate models capable of predicting post-radical surgery prognosis for ICC. Additionally, these models were compared with those developed by the American Joint Committee on Cancer (AJCC) 8th edition staging system. Notably, in the model interpretation, AR significantly reduces the risk of recurrence and mortality. Therefore, multiple models were developed, including deep learning, to explore personalized surgical recommendation models to enhance patient prognosis. We encapsulate the algorithm as a program and upload it to GitHub. The decision-making procedure in these models was analyzed to gain valuable insights into the factors influencing the prognosis of ICC.

2. Patients and Methods

2.1. Patients

Data were gathered from five hospitals (Fujian provincial hospital 218 patients, First affiliated hospital of Fujian medical university 163 patients, Fujian medical university union hospital 117 patients, The second affiliated hospital, Fujian medical university 133 patients, Mindong hospital affiliated to Fujian medical university 49 patients). To gather a comprehensive dataset, three hospitals in Fuzhou were used as the training-validation set, while the remaining data were used as the external test set. To ensure appropriate patient follow-up for at least 2 years, the collected data encompasses a period beginning from January 2021 to January 2023. Within this period, an event-free outcome was defined as no death in 2 years and no recurrence in 1 year.

The inclusion criteria for this study were as follows: *i*) confirmation of ICC through postoperative histopathology; *ii*) initial treatment was surgical resection (involving either AR or NAR); *iii*) patients with R0 margins. Conversely, the exclusion criteria were as follows: *i*) patients with severe underlying diseases; *ii*) patients with pre-resection metastases; *iii*) patients who passed away within 30 days of surgery; *iv*) patients who died to causes other than disease under investigation. An overview of the study workflow is depicted in Figure 1.

2.2. Definition of anatomic resection

AR was defined as the complete removal of the Couinaud segment, which included procedures like segmental hepatectomy, lobectomy, or hemihepatectomy. On the other hand, NAR was defined as the partial removal of portal tributaries associated with the affected segment. This classification includes procedures involving partial resection and tumor enucleation (*17,18*).

2.3. Development and validation of models

Following data preprocessing, 11 machine learning algorithms were applied to each of the 8 feature selections to predict recurrence and mortality in ICC. Subsequently, the top three models with the highest Area Under the Curve (AUC) for each feature were selected to explore the integrated model. The single model with the highest AUC, the integrated model, and the TNM-based model were evaluated through cross-validation and their performance on the external validation dataset. In this regard, the receiver-operator characteristic (ROC) curve, AUC, and decision curve analysis (DCA) were employed as indicators. The integrated model was selected when it outperformed other models in various aspects. Conversely, when a single algorithm exhibited superior performance and high AUC, it was selected as the ultimate model. Furthermore, for each feature set, the model with the highest AUC was selected for model interpretation and variable importance ranking. In the present study, AR was selected as an important parameter in all features for predicting recurrence and mortality. The analysis revealed that AR correlates with the probability of recurrence and mortality in ICC patients. To address the risk of overfitting in deep learning, the prior training-validation set was utilized for the training set, and the external validation set was utilized for the validation set in the surgical recommendation model. After excluding intraoperative and postoperative variables, the variables jointly selected by 8 feature selections were incorporated into the prediction models for surgical modality. The models were achieved using DeepSurv (*19*), neural network multitask logistic regression (N-MTLR) (*20*), and Kernel support vector model (SVM) as the base models. Hazard ratio (HR), median overall survival (OS), and significance were determined through log-rank tests for eligible recommended treatments. Subsequently, the appropriate recommended treatment model was employed for individual predictions, and the respective eligible populations for AR and NAR were summarized for personalized forecasts. The calculation of HR was modified utilizing the inverse probability of treatment weighting (IPTW) method to balance potential selections between AR and NAR for patients (*21*).

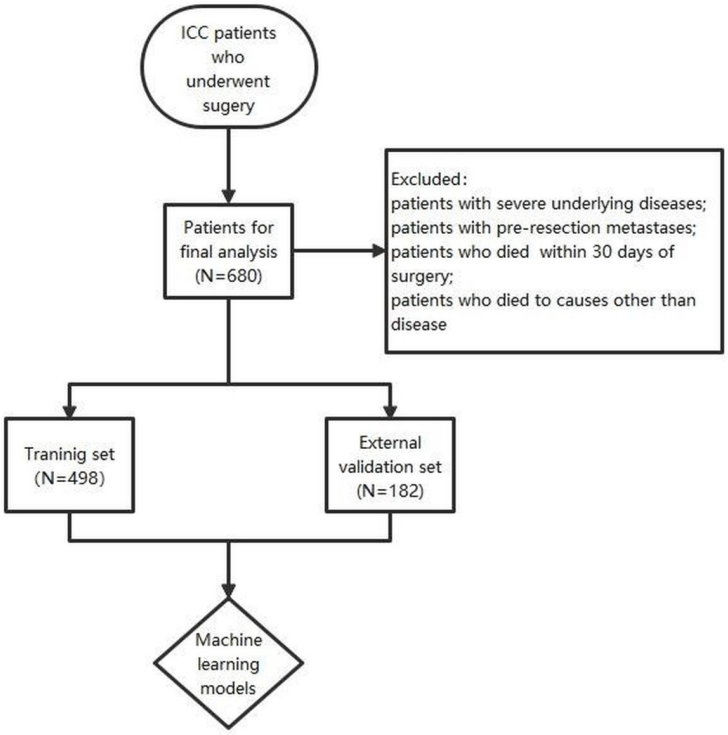

Figure 1. The overall flowchart of the study.

2.4. Statistics analysis

All analyses were carried out using Python 3.7 and R 4.1.3. $P < 0.05$ was considered Statistically significant. Details of data preprocessing, modeling, and validation approaches are presented in Supplemental Data (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*).

3. Results

3.1. Patient characteristics

The study involved 680 patients with a median follow-up of 932 days. The training-validation dataset consisted of data from 498 patients, and the data for the remaining 182 patients were used as the external test dataset. Patient demographic and clinical parameters are summarized in Table 1, indicating the external test dataset had higher percentages of patients with hepatolithiasis (56.0% *vs.* 53.8%) and TNM8 N1-stage (40.1% *vs.* 34.1%). On the other hand, some indicators were lower in the external test dataset in comparison with the training dataset, including TNM8 T1a-stage (11.5% *vs.* 15.1%) and AR (42.8% *vs.* 62.9%).

3.2. Model construction, validation, and interpretation for predicting prognosis

Following data preprocessing, 19 continuous and 7 discrete features were used in machine learning. Since adjuvant chemotherapy after surgery for ICC has become a standard treatment, 672 patients (99%) in this study cohort received standard adjuvant chemotherapy, with only 8 patients not receiving chemotherapy. Given the high consistency of adjuvant chemotherapy in this study, chemotherapy was not included as an independent variable in the analysis. The features retained after each feature selection method are shown in Supplemental Table S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*). The results obtained from incorporating machine learning algorithms and feature sets are shown in Figure 2. The presented heatmaps illustrate AUC for various combinations of machine learning algorithms and feature selection methods. Meanwhile, the nested cross-validation approach was utilized to optimize model hyperparameters and evaluate models. Evaluations of the benchmark model, single models, and integrated model on the training-validation and external test datasets are presented in Figure 3, Supplemental Figure S1 and Table S2 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*). In the context of the recurrence and mortality prediction table, despite some overlap in the confidence intervals of the baseline model, the proposed model demonstrated superior performance (Table 2). More specifically, Figure 4 and Supplemental Figure S6-S7 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*) indicate that the integrated model exhibited enhanced consistency in both the calibration curve and DCA for both recurrence and mortality. While there were negligible deviations in the AUC for the recurrence model between the integrated and single models, the integrated model outperformed

Table 1. Demographic and clinical parameters for combined training-validation and test datasets (before imputation)

Parameter	Combined Training & Validation Sets (*n* = 498)	External Test Set (*n* = 182)	*p* value
Age, median (IQR), year	61 (54.0-67.0)	64.5 (55.0-70.0)	< 0.001
Sex, *n* (%)			0.17
Female	234 (47.0)	97 (53.2)	
Male	264 (53.0)	85 (46.7)	
BMI, median (IQR), Kg/m²	22.890 (20.9,24.4)	23.1800 (21.5,24.9)	0.1
Missing, *n* (%)	7 (1.4)	4 (2.1)	
Hepatolithiasis, *n* (%) (I)			0.66
Yes	268 (53.8)	102 (56.0)	
No	230 (46.2)	80 (44.0)	
Vascular invasion, *n* (%) (I)			0.6
Yes	236 (47.4)	90 (49.5)	
No	263 (52.6)	92 (50.5)	
Acute cholangitis, *n* (%)			< 0.001
Yes	208 (41.8)	113 (62.1)	
No	290 (58.2)	69 (37.9)	
TNM8 T stage, *n* (%)			0.19
T1a	75 (15.1)	21 (11.5)	
T1b	60 (12.0)	27 (14.8)	
T2	48 (9.6)	27 (14.8)	
T3	252 (50.6)	82 (45.1)	
T4	63 (12.7)	25 (13.7)	
TNM8 N stage, *n* (%)			0.18
N1	170 (34.1)	73 (40.1)	
N0	328 (67.2)	109 (59.9)	
Tumor distribution, *n* (%)			0.19
Left hemiliver	257 (51.6)	83 (45.6)	
No	241 (48.3)	99 (54.4)	
Maximum tumor diameter, median (IQR), cm	5.0 (3.5,7.0)	4.85 (3.4, 7.0)	0.7
Anatomic resection, *n* (%)			< 0.001
Yes	313 (62.9)	78 (42.8)	
No	185 (37.1)	104 (57.1)	
Operative blood loss, median (IQR), mL	400 (200, 600)	450 (200, 700)	0.81
Missing, *n* (%)	15 (3.0)	5 (2.7)	
Number of lymphatic dissection, *n* (%)	5 (3.7)	5 (4.8)	0.23
Neutrophil ratio, median (IQR), %	87.8 (84.2, 90.6)	88.6 (84.9, 91.3)	0.12
Missing, *n* (%)	17 (3.4)	0 (0.0)	
Lymphocyte ratio, median (IQR), %	6.3 (4.6, 8.5)	6.60 (4.9, 8.8)	0.47
*Lymphocyte count, median (IQR), 10^9/L	0.80 (0.6, 1.1)	0.8950 (0.6, 1.2)	0.14
Missing, *n* (%)	17 (3.4)	5 (2.7)	
HB, mean(IQR), g/L	112 (97.0, 127.0)	108.0 (96.0 , 124.5)	0.13
Missing, *n* (%)	33 (6.6)	19 (10.4)	
*WBC count, median (IQR), 10^9/L	12.77 (10.1, 15.1)	13.350 (10.4, 15.8)	0.2
Missing, *n* (%)	9 (1.8)	0 (0.0)	
*PLT count, median (IQR), 10^9/L	186 (139.0, 232.0)	198. 0 (145.5, 240.5)	0.15
Missing, *n* (%)	3 (0.6)	7 (3.0)	
CA199, median (IQR), U/mL	80.4 (12.9,449.9)	83.1 (14.9, 611.3)	0.61
CA125, median (IQR), U/mL	10.4 (4.1,28.2)	9.9 (3.8, 27.1)	0.76
Missing, *n* (%)	78 (15.7)	44 (24.2)	
CEA, median (IQR), ng/mL	2.9000 (1.4,5.4)	3.0450 (1.5, 5.7)	0.67
ALB, median (IQR), g/L	29.9 (26.0,33.1)	29.8 (26.0, 32.9)	0.63
Missing, *n* (%)	1 (0.2)	1 (0.5)	
DBIL, median (IQR), umol/L	9.450 (5.4,19.9)	9.40 (5.7, 23.0)	0.77
IBIL, median (IQR), umol/L	11.500 (7.3,19.4)	11.450 (7.4, 18.0)	0.8
ALP, median (IQR), U/L	102.0 (70.0,212.5)	115.0 (73.0, 228.5)	0.32
Missing, *n* (%)	49 (9.8)	10 (5.5)	
GGT, median (IQR), U/L	114 (76,201)	120.9550 (73.0, 228.5)	0.27
Missing, *n* (%)	29 (5.8)	0 (0.0)	
Recurrence at 1 year, *n* (%)	274 (55.0)	114 (62.6)	0.081
Death at 2 years, *n* (%)	249 (50.0)	96 (52.7)	0.55
Median length of OS	739.50 (432.25, 1125.25)	831.5 (656.0, 1201.0)	< 0.001

Only features used in modeling are presented. Categorical data are summarized with median, percentages, and p-values pertaining to Fisher's exact test. Continuous data are summarized with median and IQR, and p-values pertain to the Wilcoxon rank sum test. Variables marked with (I) were based on preoperative imaging studies, while all other tumor-related variables were based on histopathological examination. *Abbreviations*: IQR, interquartile range; BMI, body mass index; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; HB, hemoglobin; WBC, white blood cell; PLT, platelet; ALB, albumin; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase.

Table 2. AUC with 95% confidence intervals for each prediction model's validation and external test dataset

Outcome	Validation set		External test set	
	AUC	95% CI	AUC	95% CI
OS				
Single model	0.949	0.912-0.974	0.848	0.791-0.907
Integrated model	0.923	0.913-0.942	0.917	0.887-0.951
TNM based model	0.841	0.813-0.878	0.857	0.804-0.917
Recurrence				
Single model	0.893	0.861-0.924	0.946	0.918-0.981
Integrated model	0.918	0.903-0.937	0.877	0.838-0.919
TNM based model	0.807	0.773-0.842	0.825	0.764-0.887

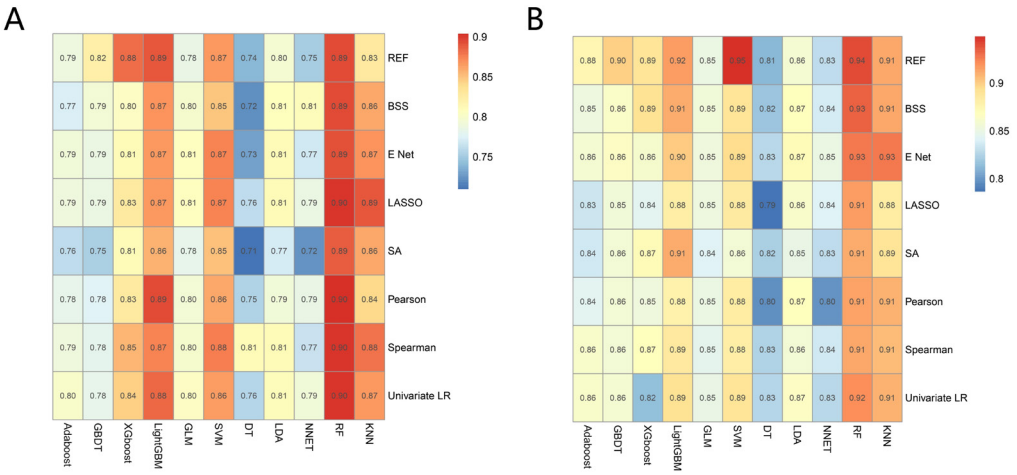

Figure 2. Heatmaps illustrating the performance of each machine learning algorithm (columns) with each feature reduction method (rows). **(A)** Heatmap for predicting recurrence; **(B)** Heatmap for predicting overall survival. *Abbreviations*: RFE, recursive feature elimination; BSS, best subset selection; E Net, elastic net; LASSO, least absolute shrinkage and selection operator; SA, simulated annealing; Univariate LR, univariate logistic regression; AdaBoost, adaptive boosting machine; GBDT, gradient boosting decision tree; XGboost, extreme gradient boosting machine; LightGBM, light gradient boosting machin; GLM, generalised linear model; SVM, support vector machine; DT, decision tree; LDA, linear discriminant analysis; NNET, neural network; RF, random forest; KNN, K nearest neighbours.

single models in terms of DCA and AUC for mortality. Considering the complexity and efficiency of the model implementation, random forest (RF) was used for recurrence, while the integrated model of SVM, RF, and K-nearest neighbors (KNN) was used for OS. When ranking the importance of both recurrence and mortality variables, AR held a more critical position. The models were further explained through the Shapley additive explanations (SHAP) analysis (Supplemental Figure S2 and S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*). The analysis indicates that the presence of vascular invasion and hepatolithiasis in patients increases the mortality rate, while AR reduces the mortality rate. In SHAP analysis of recurrence and mortality, operative blood loss exhibited unstable patterns across various models. This parameter can either increase or decrease the outcome variable.

3.3. Construction of a surgical prediction model

Given the significant importance of AR in SHAP analysis and the results of previous feature screening, data on BMI, CA199, presence of vascular infiltrates and hepatolithiasis on imaging, and AR were included in the surgical approach recommendation models. Hyperparametric search results for each model are shown in Supplemental Table S3-S4, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*). The N-MTLR model recommended treatments that were associated with significantly higher survival in both the training and validation datasets (Table 3 and Figure 4), with HR of 0.333 (95% CI: 0.262-0.424; $p < 0.001$) in the training dataset and 0.561 (95% CI: 0.357-0.882; $p = 0.012$) in the validation dataset. To consider potential patient selection differences between AR and NAR, comparisons were conducted using IPTW, with higher weight assigned to underrepresented patients in each treatment group. IPTW results showed a performance similar to that of conventional HR. In the DeepSurv, N-MTLR model, and Kernel SVM models, AR was recommended for 571 (84.0%), 493 (72.5%), and 304 (44.7%) patients, respectively. Among patients with hepatolithiasis, AR was recommended for 199 (53.8%) patients. Notably, in the subgroup of patients with both hepatolithiasis and vascular invasion, surgical recommendations based on the N-MTLR model also

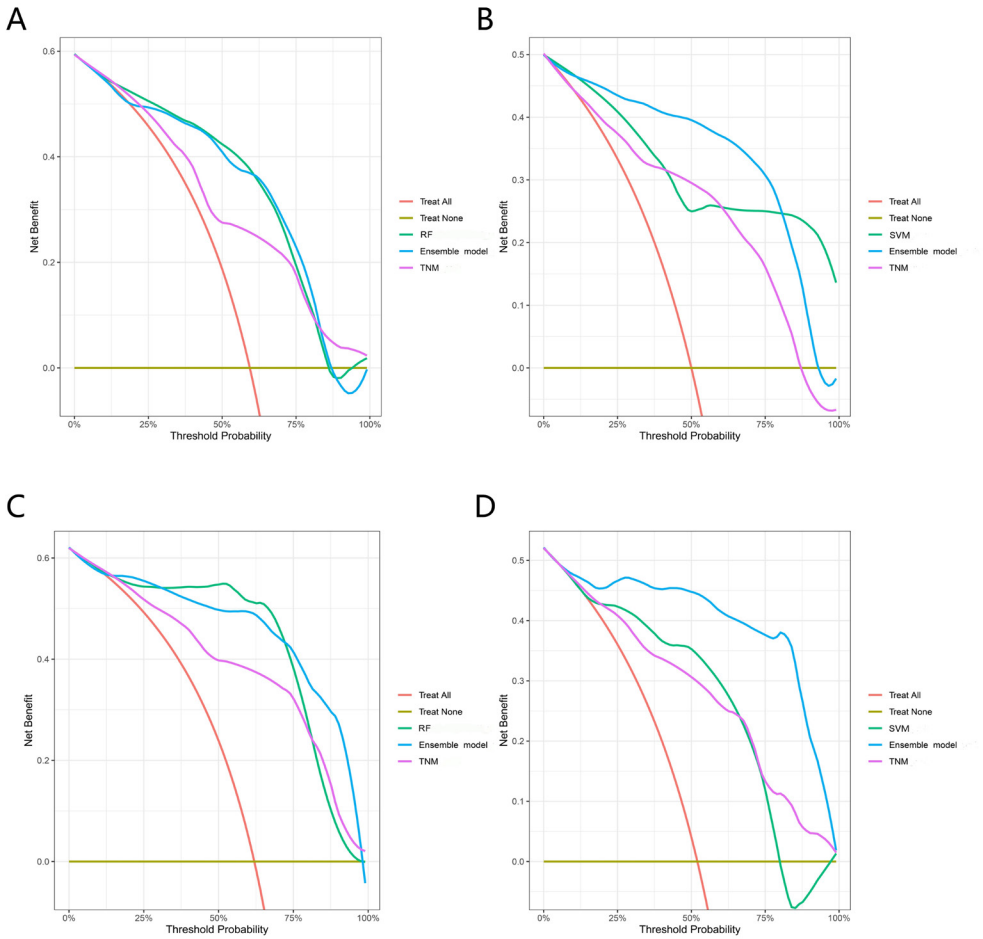

Figure 3. The DCA curves for single algorithms with the highest AUC, the ensemble model, and the baseline model in the nested cross-validation (A-B) and external validation dataset (C-D). (A) The DCA curves for predicting recurrence in the nested cross-validation; **(B)** The DCA curves for predicting overall survival in the nested cross-validation; **(C)** The DCA curves for predicting recurrence in the external validation dataset; **(D)** The DCA curves for predicting overall survival in the external validation dataset.

Table 3. Survival predictions for treatment according to model recommendations

Model	Validation set		HR (95% CI)	*p* value	HR, IPTW (95% CI)	*p* value
	Patients receiving recommended treatment	Patients not receiving recommended treatment				
N-MTLR						
Development Set	980.0 (812.0)	567.0 (478.0)	0.333 (0.262, 0.424)	< 0.001	0.409 (0.316, 0.528)	< 0.001
Validation Set	858.0 (259.0)	769.0 (666.0)	0.561 (0.357, 0.882)	0.011	0.597 (0.386, 0.925)	0.021
DeepSurv						
Development Set	815.0 (99.0)	862.0 (603.0)	0.919 (0.780, 1.251)	0.91	2.269 (1.590, 3.238)	< 0.001
Validation Set	792.0 (745.0)	701.0 (673.0)	0.8602 (0.490, 1.510)	0.60	1.205 (0.605, 2.402)	0.59
Kernel SVM						
Development Set	637.0 (709.0)	740.0 (694.0)	3.662 (2.000, 6.709)	0.053	6.703 (3.478, 12.918)	< 0.001
Validation Set	821.0 (52.0)	832.0 (559.0)	1.722 (0.987, 3.005)	0.39	2.236 (1.335, 3.746)	0.0022

Abbreviations: HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; N-MTLR, neural multitask logistic regression; OS, overall survival; SVM, Support Vector Machine. HRs are given for the patients who received the recommended treatment compared with those who did not.

demonstrated benefits for patients (Supplemental Figure S8, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=227*). In cases of confirmed hepatolithiasis without vascular invasion on imaging, AR was recommended for 12 (8.5%) patients. The procedure for integrating the recommendation model is available at *https://github.com/haizhili/Prognostic_Prediction_and_Surgical_Guidance_for_ICC*.

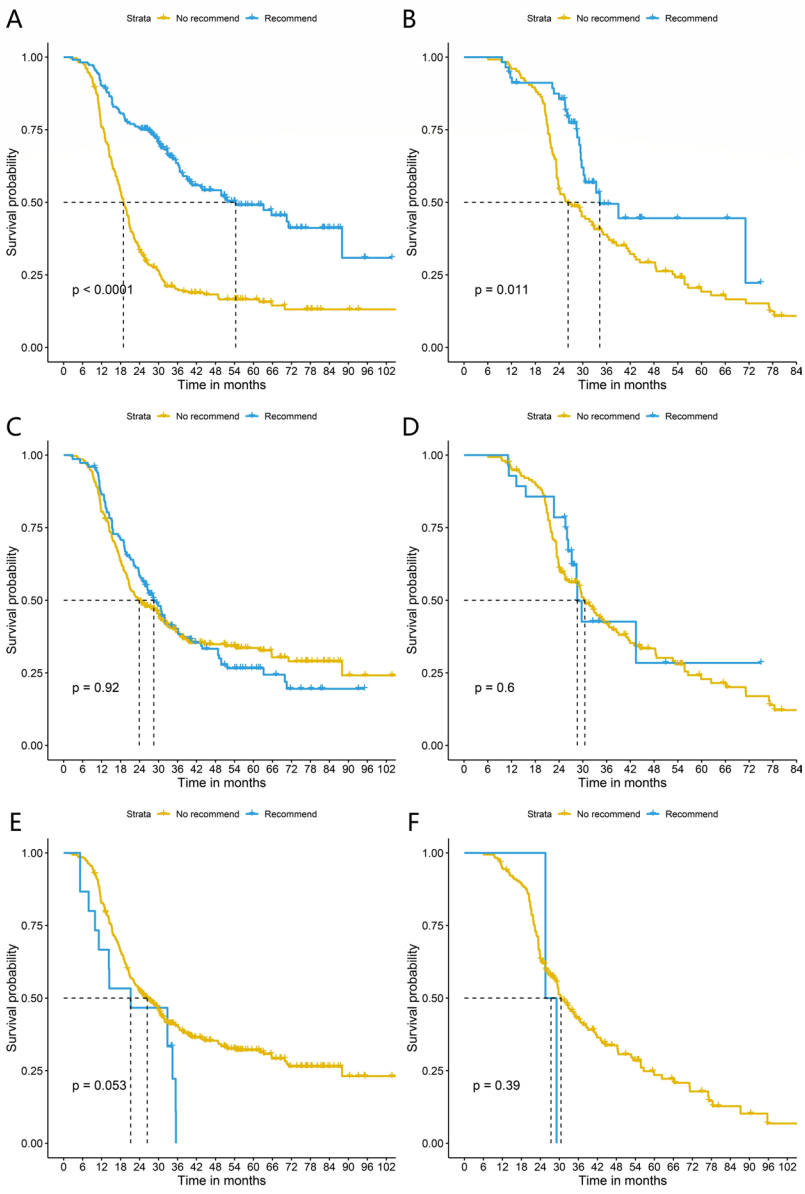

Figure 4. Results for (A-B) N-MLTR, (C-D) DeepSurv, and (E-F) Kernel SVM models. **(A)** The Kaplan-Meier curves for the N-MLTR model in the training dataset; **(B)** The Kaplan-Meier curves for the N-MLTR model in the validation dataset; **(C)** The Kaplan-Meier curves for the DeepSurv model in the training dataset; **(D)** The Kaplan-Meier curves for the DeepSurv model in the validation dataset; **(E)** The Kaplan-Meier curves for the Kernel SVM model in the training dataset; **(F)** The Kaplan-Meier curves for the Kernel SVM model in the validation dataset.

4. Discussion

In the present multicenter study, an incremental analysis was conducted. In the first step, multiple machine learning algorithms and various dimensionality reduction techniques were compared using routine medical data to develop and validate predictive models. These models can effectively and precisely predict recurrence and OS. AR emerged as a variable, consistently appearing in all feature selections. It is worth noting that AR is a variable with strong correlations with both the recurrence and OS. Furthermore, considering the importance of explaining medical decisions to patients, the models with the highest AUC for each feature selection were interpreted. These interpretations consistently highlighted the risk-reducing effects of AR on both recurrence and mortality, reflecting its overall benefit in the population. However, it should be indicated that the model interpretation focuses on the overall benefit of AR in the population but fails to analyze the advantages of NAR, which remains valuable in real-world clinical practice (*22,23*). Therefore, in the second step, surgical modality recommendation models were developed for both AR and NAR, including deep learning techniques, to enable individual-level predictions. The findings revealed that the majority of patients were suitable candidates for AR. Meanwhile, it was found that individuals who could be ideal candidates for NAR were also considered suitable candidates for AR. This refinement in population characteristics provides valuable insights for clinical practice.

Accurate prediction of postoperative recurrence and survival among ICC patients holds critical importance (*24,25*). Although AR has demonstrated improved outcomes in HCC, revealing its benefits in ICC requires further investigations (*10,11*). Conventional treatment decisions typically encounter some shortcomings, including poor personalization, and dependence on physician preference and group-level data (*12-14*). To

resolve these shortcomings and accurately predict ICC recurrence and survival, numerous predictive models using routine clinical data have been developed. Notably, a model based on the N-MTLR model was introduced, providing personalized surgical recommendations. This advancement benefits patients and assists physicians in making treatment decisions, thereby improving ICC care. The AUC values of various machine learning models for predicting recurrence and OS remain consistent across combined training-validation and external validation datasets. Minor performance variations were observed in OS models during cross-validation and validation on the external validation datasets. These variations were especially more pronounced through recursive feature selection. However, these models consistently outperformed the TNM-based prognostic model. An additional advantage of the developed models lies in the use of integrated modeling. Integrated models can enhance the final predictive performance beyond individual predictive models. This enhancement is achieved by combining diverse predictive models that have been trained using distinct architectures and hyperparameters. The integration of individual classifiers in a parallel manner increased consistency across various datasets. Notably, integrated models are not sensitive to the challenges imposed by the "curse of dimensionality", where the predictive or discriminative efficacy of a model rapidly declines as the data dimensionality increases (*26-28*). It is worth noting that classical models were employed in the present study to predict recurrence, which can provide clear explanations for their predictions. In the medical field, model explanation facilitates understanding reasons for making particular decisions.

This article employs several classical feature selection methods such as annealing, recursive feature elimination, optimal subset, and correlation coefficient to select variables. These methods are used to determine variables from different perspectives, which can improve the accuracy and generalization ability of prognostic models and reduce overfitting (*29*). Moreover, AR was screened out in different feature selection methods, indicating that it is statistically significant. Meanwhile, the model interpretation showed that AR affects the survival of patients with ICC. Therefore, several variables were used after removing intraoperative and postoperative variables, most often screened out by feature engineering as inputs to the surgery recommendation model.

In the model interpretation, it was observed that AR and the absence of hepatolithiasis and vascular invasion may have positive effects on the prognosis of ICC patients. However, other variables such as BMI may also affect the outcome differently, suggesting that the effect of the same variable on the result is not unique across models (*22,23*). Accordingly, it was inferred that AR does not benefit all patients and an individual-level analysis of individuals who were recommended AR to gain a deeper understanding of its applicability.

In this study, the surgical recommendation model based on the N-MTLR model indicated that 493 patients (72.5%) might be suitable candidates for AR. Unlike previous population-based studies that relied on a single standard, the proposed model comprehensively considered multiple crucial preoperative variables, providing more detailed suggestions for individualized decision-making. Overall, AR demonstrated significant advantages in terms of recurrence and survival rates for most patients, particularly for those with larger tumors and without liver dysfunction, making it the more appropriate surgical option. However, the model also showed that non-anatomic resection (NAR) might be a better option for certain patient groups. NAR offers advantages such as being less invasive, preserving more liver tissue, and promoting faster postoperative recovery. Specifically, for patients with smaller tumors, NAR and AR showed minimal differences in recurrence and survival rates, and NAR could reduce unnecessary liver tissue removal, preserving more liver function. Additionally, NAR proved beneficial for patients with limited liver function (*e.g.*, those with cirrhosis or other chronic liver diseases), significantly reducing the risk of postoperative liver failure while maintaining a high survival rate. Among 42 patients (13.0%) with vascular invasion detected through imaging, NAR may also be the more appropriate choice. It should be noted that hepatolithiasis is classified as a poor prognostic factor for ICC, though further studies are needed to determine the best surgical approach for ICC patients with hepatolithiasis. In clinical practice, AR is typically used to resect biliary lesions associated with stones. However, the study showed that 46.2% of ICC patients with hepatolithiasis (171 patients) might be more suitable candidates for NAR, highlighting the importance of individualized treatment decisions.

The current approach to clinical decision-making often relies on physician preference and group-level evidence-based clinical practices to advise patients. However, this method of decision-making may not always offer the most suitable treatment options for individuals and may not effectively incorporate the unique characteristics of each patient. However, clinicians can employ various algorithms to provide individualized treatment recommendations for patients (*16,30,31*). Researchers typically use clinical data to investigate the benefits of AR and NAR. For instance, investigations reveal that patients with ICC combined with hepatolithiasis benefit more from AR than NAR (*32*). In the developed model, only 12 patients (8.5%) with hepatolithiasis and no vascular invasion were considered suitable candidates for AR. In contrast to conventional machine learning research that primarily focuses on predicting prognosis, this article focuses on developing a personalized surgical modality recommendation algorithm. This algorithm not only

enhanced patient outcomes but also can be encapsulated in a compact executable file on computers. This feature simplifies its clinical application for healthcare providers. The proposed recommendation model used routine clinical data, facilitating its application and disseminating the research. Meanwhile, instead of traditional nomogram scores, the executable file directly provides an appropriate surgical approach for the patient, which makes the output more concise and easier to use.

In addition to remarkable advantages, this study also has some shortcomings. First, the data used in this study were retrospective, potentially introducing regression bias. The interpolation method used to address missing data may affect the integrity of the clinical data, emphasizing the need for future international prospective clinical trials to validate these findings. Secondly, the data used in this article did not incorporate information from radiomics. As a result, more advanced imaging-based models may outperform the proposed model. However, this model utilized routine preoperative and postoperative examination results as input data, which effectively minimized the additional time and costs typically associated with data preparation and processing. This approach also simplifies replication in primary care hospitals. Finally, while the absence of specific data regarding postoperative adjuvant treatments in the raw data might affect the results, it is important to note that more than 99% of the patients in this study received standard postoperative adjuvant chemotherapy. The high consistency of adjuvant therapy within the patient population significantly reduced the potential impact of such treatments on the comparison between surgical approaches (AR and NAR). This consistency enhanced the model's applicability and reliability in this standardized treatment population. The present study provides guidance for developing models focusing on surgical procedure data.

In conclusion, this article compares various machine learning algorithms and feature selection methods to develop two predictive models for recurrence and OS following radical resection in ICC patients. The results demonstrate that the developed model outperforms conventional approaches. Additionally, an advanced preoperative surgical recommendation system based on clinical data was introduced. This model enhances patient-centered decision-making and suggests personalized treatments. The recommended surgical approach exhibited significant improvements in patient prognosis. This study offers fresh insights into the clinical application of surgical procedures for ICC, emphasizing the potential for more effective treatment strategies.

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Original Article

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First-line systemic therapy and sequencing options in advanced biliary tract cancer: A systematic review and network meta-analysis

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SUMMARY The current state of systemic therapy for advanced biliary tract cancer (BTC) has undergone significant changes. Currently, there are no clinical trials directly comparing various first-line systemic therapy regimens to each other, and these trials are unlikely to be conducted in the future. In this systematic review, after various abstracts and full-text articles published from the establishment of the database until October 2024 were searched, we included and analysed phase 3 clinical trials to evaluate the efficacy of different first-line systemic treatment regimens in advanced BTC. We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and a random effects model to pool the overall effects. Finally, seven low-risk-of-bias trials (with all of the trials representing first-line trials) were included. A total of 4033 patients were included in seven first-line trials. In terms of progression-free survival (PFS), network meta-analysis revealed that durvalumab + gemcitabine + cisplatin (GemCis) triple therapy, S-1 + GemCis triple therapy, and pembrolizumab + GemCis triple therapy were superior to GemCis. In terms of overall survival (OS), network meta-analysis revealed that durvalumab + GemCis triple therapy and pembrolizumab + GemCis triple therapy outperformed GemCis. According to the ranking of the P scores, durvalumab + GemCis triple therapy ranked first in PFS and second in OS. Therefore, the advantages of molecular immunotherapy have gradually become known, which suggests that future trials should focus on other potential combinations and molecular immunotargeted therapies.

Keywords cholangiocarcinoma; chemotherapy; immunotherapy; durvalumab; P-score

1. Introduction

Biliary tract carcinoma (BTC) is a rare malignant tumour with a dismal prognosis (*1*). Most cases are identified at an advanced stage, and surgical removal is not an option for treatment (*2*). For advanced BTC, chemotherapy is the first-line treatment. Immune checkpoint inhibitors (ICIs) and molecular-targeted treatment have become viable options for systemic therapy for advanced BTC as a result of the advancement of molecular-targeted therapy technologies driven by next-generation sequencing (NGS) (*3*). Additionally, systemic therapy can be used in conjunction with local therapy, such as radioembolization (*4*), hepatic arterial infusion (HAI) of chemotherapy (*5*), and transarterial (chemo) embolization (*6*). Patients with unresectable BTC have a median overall survival (OS) of approximately one year, and the 5-year survival rate is less than 10% (*7,8*).

In the previous decade, doublet chemotherapy with gemcitabine and cisplatin (GemCis) was thought to be the most successful first-line treatment of this condition(*9,10*). Treatment choices will become limited as the illness progresses, and fluorouracil-based combination therapy has demonstrated only moderate effectiveness (*11,12*). More alternatives for second-line BTC treatment are now available due to the increased focus given to personalized precision treatment based on gene and molecular targeted detection methods. According to research performed in second-line or later settings, patients with cancers that have certain molecular abnormalities, such as fibroblast growth factor receptor (FGFR)-2 fusions (*13,14*) and isocitrate dehydrogenase (IDH)-1 mutations (*15,16*),

may benefit from ICIs or targeted therapies. However, unique molecular subpopulations are uncommon, and chemotherapy is the only available therapeutic choice for the majority of individuals (*17*).

As research has progressed, GemCis is no longer the only option for first-line systemic treatment of advanced BTC. Many regimens are just as effective as GemCis, including capecitabine + oxaliplatin (XELOX) combination therapy (*18*), S-1 + gemcitabine combination therapy (*19*), pembrolizumab + GemCis triple therapy (*20*), durvalumab + GemCis triple therapy (*21*), S-1 + GemCis triple therapy (*22*), and nab-paclitaxel + GemCis triple therapy (*23*). Both durvalumab and pembrolizumab are immune agents; however, the tumour microenvironment of most BTCs is characterized by immunosuppression or immune rejection(*24*), thus resulting in a relatively low response to immunotherapy alone in advanced BTCs (*25,26*). The triple immunization regimen against advanced BTC has demonstrated better results, which may be due to the regulation of the immune system by GemCis *via* a direct immune stimulation mechanism, which downregulates the immunosuppressive microenvironment and increases immunogenicity (*27,28*).

However, until now, there have been no clinical trials comparing various first-line systemic treatment options, and no conclusive data have demonstrated which option is preferred. A network meta-analysis (NMA) is useful for comparing different drugs across randomized clinical trials (RCTs) because these studies demonstrate varying efficacy across lines of therapy (*29,30*). This scenario is particularly crucial because the recommendations that are currently in place only list the available therapies without addressing which therapies should be prioritized. In this systematic review and network meta-analysis, we ranked the effectiveness of several first-line systemic treatments (which must be indirectly compared with GemCis) in the treatment of advanced BTC.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard was followed in the reporting of this systematic review (*31*). Due to the fact that this was not a meta-analysis of individual patients, the informed consent requirements were not met, and institutional review board permission was not needed.

2.1. Study objective

The objective of the current study was to evaluate the effectiveness of several first-line systemic therapy regimens (wherein GemCis is a necessary component) in patients with advanced BTC.

2.2. Eligibility Criteria

Phase 3 randomized clinical trials for first-line systemic treatment of advanced BTC malignancies were included in the analysis (with the regimens including GemCis).

2.3. Data Sources and Search Strategies

An extensive search of the literature was performed in the PubMed and Web of Science databases for abstracts and full-text articles that fit the criteria. PFS and OS for all of the patients receiving first-line therapy represented the outcomes of interest.

2.4. Study Selection

Relevant abstracts and full-text papers were identified *via* the title list, and these abstracts and papers were subsequently examined.

2.5. Data Extraction

Prespecified data, such as sample sizes, baseline characteristics, and utilized therapies, were extracted from each study *via* a standardized data abstraction form.

2.6. Risk of Bias and Certainty of Evidence

The Cochrane Collaboration tools(*32*) were used to assess the likelihood of bias in trials in the following areas: random sequence generation, assignment hiding, blind techniques, incomplete outcome data, and selective outcome reporting. The GRADE process (Grading of Recommendations, Assessment, Development and Evaluation) was used to evaluate the certainty of the evidence (*i.e.*, the certainty of the estimate) (*33*).

2.7. Statistical Analysis

R statistical software (version R 4.3.2) was used to conduct the statistical analysis for this study. The results were represented by logarithmically converting the predicted hazard ratios (HRs) with matching 95% confidence intervals (CIs) that were collected from the included trials. A random effect network meta-analysis under the frequentist framework was used to compare mixed treatments (*34*). League tables and forest graphs were produced by the network estimation process of the reverse transformation. Cochran's Q was used to evaluate heterogeneity between and within designs, and I^2 statistics were used to quantify heterogeneity. The I^2 values for low, moderate, and high levels of heterogeneity were less than 25%, 25% to 75%, and greater than 75%, respectively. The ranking of the processing was performed *via* P scores, which

are represented as frequency analogues under the cumulative ranking curve (SUCRA) (*35*). Rankgrams were plotted against P scores to visualize treatment rankings. A better therapeutic impact was indicated by a higher P score. NMA was performed with the "netmeta" R package.

3. Results

3.1. Study Selection

By using screening techniques for electronic searches, 409 titles and abstracts were ultimately identified, and 85 of these titles and abstracts could be evaluated (Figure 1). Seven total references were found (*9,19-23,36*).

3.2. Study Characteristics

Seven identified first-line trials involved a total of 4033 patients (*9,19-23,36*). A first-line systemic chemotherapy regimen for patients with advanced BTC for the subsequent ten years was established in 2010 by the ABC-02 trial (*9*), which compared the use of gemcitabine alone with gemcitabine + cisplatin (GemCis). The GemCis dual chemotherapy regimens were compared across six trials (S-1 + GemCis, durvalumab + GemCis, pembrolizumab + GemCis, S-1 + gemcitabine, nab-paclitaxel + GemCis, NUC-1031 + cisplatin) (*19-23,36*) (Supplementary Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*). The age range of the patients included in the trials was 20-85 years (Table 1).

3.3. Network Meta-analysis

A PFS benefit was observed in the network meta-analysis when comparing durvalumab + GemCis triple therapy versus GemCis double therapy (HR, 0.75; 95% CI, 0.63–0.89), S-1 + GemCis triple therapy versus GemCis double therapy (HR, 0.75; 95% CI, 0.58–0.97), and pembrolizumab + GemCis triple therapy versus GemCis double therapy (HR, 0.86; 95% CI, 0.75–0.99). PFS was worsened with NUC-1031 plus cisplatin combination therapy (NUC-1031 is a phosphoramidate modification of gemcitabine) compared to GemCis (HR, 1.45; 95% CI, 1.21–1.73). Compared with that of GemCis double therapy, the PFS benefit of nab-

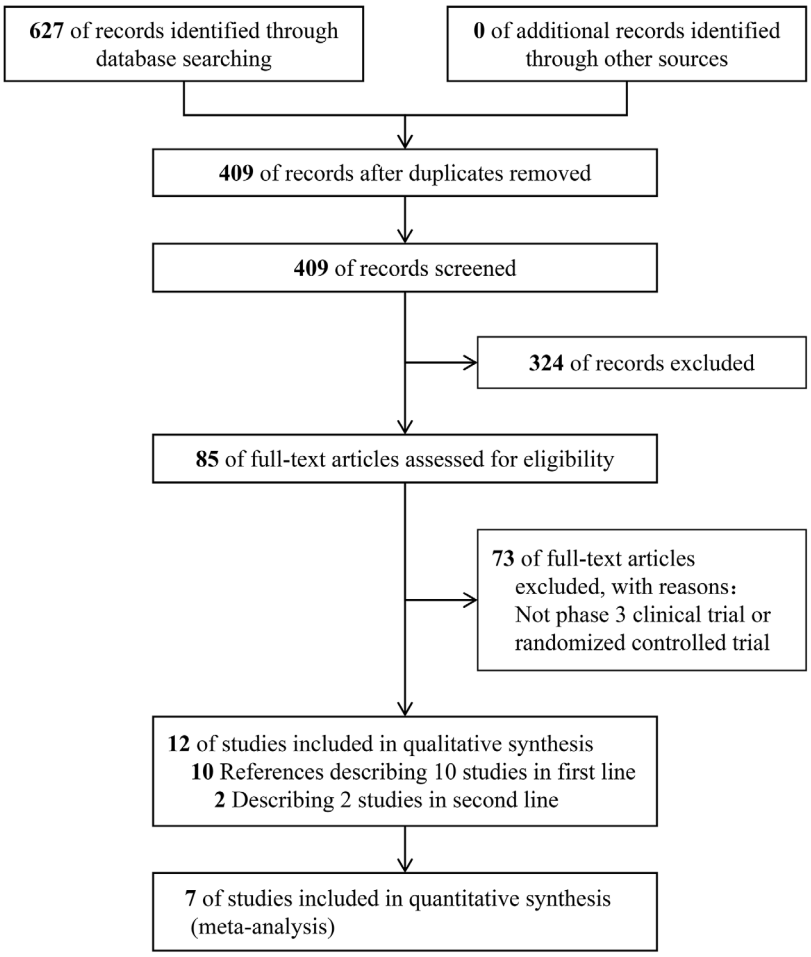

Figure 1. PRISMA flow diagram displaying the process of screening and choosing.

Table 1. Baseline characteristics for patients included in the first-line trials

Study Name	Arm	Patients	ECOG PS (0,1,2)%	Median Age (Range)	Race/Region	Sex (male %)
Valle J 2010 (ABC-02)	GemCis	204	0 (32.4%),1 (54.4%), 2 (13.2%)	63.9 (32.8-81.9)	Britain	47.10%
	Gemcitabine	206	0 (31.1%),1 (56.8%), 2 (11.7%),unknown (0.5%)	63.2 (23.4-84.8)		47.60%
Morizane C 2019 (JCOG1113)	Gemcitabine + S-1	179	0 (69.3%),1 (30.7%)	67 (27-79)	Japan	54.20%
	GemCis	175	0 (74.3%),1 (25.7%)	67 (41-78)		56.60%
Oh DY 2022 (TOPAZ-1)	GemCis + Durvalumab	341	0 (50.7%),1 (49.3%)	64 (20-84)	multinational	49.60%
	GemCis	344	0 (47.4%),1 (52.6%)	64 (31-85)		51.20%
Kelley RK 2023 (KEYNOTE-966)	GemCis + Pembrolizumab	533	0 (48%),1 (51%),2 (<1%)	64.0 (57.0-71.0)	multinational	53%
	GemCis	536	0 (43%),1 (57%)	63.0 (55.0-70.0)		51%
Rachna T 2023 (SWOG 1815)	GemCis + Nab-paclitaxel	441 (2:1)	NR	NR	NR	45%
	GemCis					
Ioka T 2023 (KHBO1401-MITS)	GemCis + S-1	246 (1:1)	0-1 (98.4%),2 (1.6%)	68 (40-84)	Japan	53.70%
	GemCis		0-1 (100%)	68 (39-81)		55.30%
Knox J 2023	NUC-1031 + Cisplatin	828 (1:1)	NR	65	NR	53.40%
	GemCis					

Abbreviation: GemCis, Gemcitabine + Cisplatin. NR, not reported. ECOG PS: ECOG performance-status score, ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

paclitaxel + GemCis triple therapy and gemcitabine + S-1 double therapy was not inferior (Figure 2 and Supplementary Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

In terms of improving OS, the combination of durvalumab + GemCis triple therapy (HR, 0.80; 95% CI, 0.66–0.98) and pembrolizumab + GemCis triple therapy (HR, 0.83; 95% CI, 0.72–0.95) was superior to GemCis combination therapy. Compared with those of GemCis, the OS benefits of nab-paclitaxel + GemCis, S-1 + gemcitabine, and GemCis + S-1 were noninferior (Figure 2 and Supplementary Table S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

The highest durvalumab + GemCis ranking for PFS (P score = 87.81%) and the highest S-1 + GemCis ranking for OS (P score = 81.43%) matched these results (Figure 3 and Supplementary Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

3.4. Risk of Bias and Certainty of Evidence

Via the Cochrane method for assessing the risk of bias, a qualitative assessment was performed by evaluating several indicators for each unique study. With two trials blindly assessing the outcome evaluators and the remaining trials either not performing blind assessments or not clearly performing blind assessments, the trial was deemed to have overcome the overall low-risk bias (Figure 4). The certainty of indirect comparative evidence was deemed to be generally high (Supplementary Table S4 and S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

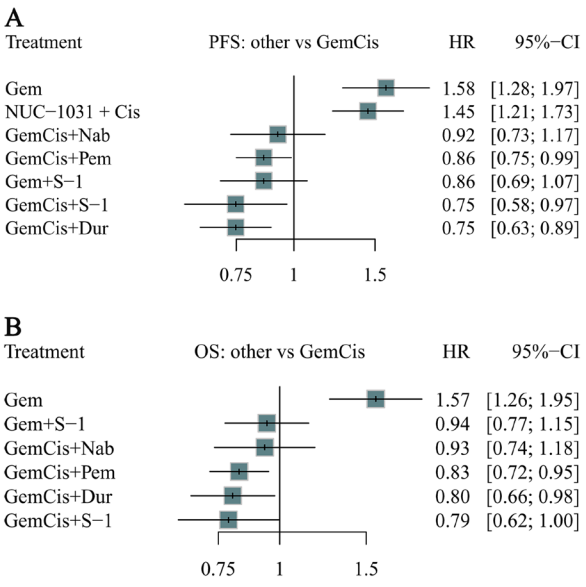

Figure 2. Forest plot of Frequentist network meta-analysis using random-effects model. (A) Progression-free survival (PFS). **(B)** Overall survival (OS). *Abbreviation*: Gem: gemcitabine; Cis: cisplatin; GemCis: gemcitabine + cisplatin; Nab: nab-paclitaxel; Pem: pembrolizumab; Dur: durvalumab.

4. Discussion

The prognosis for advanced BTC patients is currently poor, and patients can respond differently to various

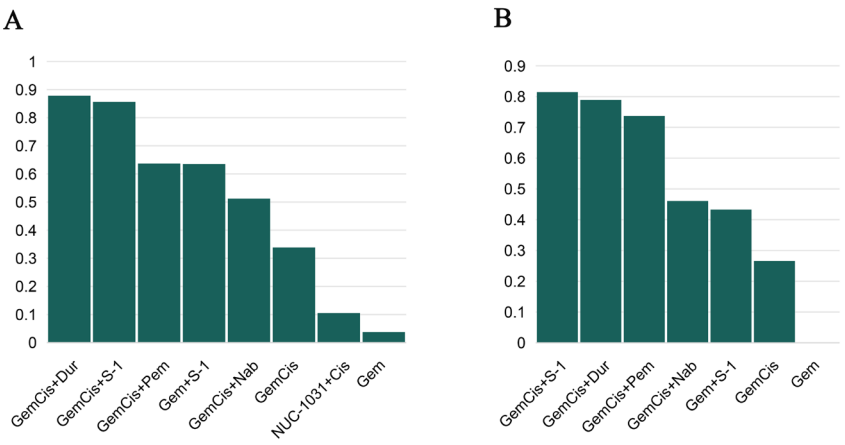

Figure 3. Ranking of 1st line treatments. (A) Progression-free survival (PFS). **(B)** Overall survival (OS). *Abbreviation*: Gem: gemcitabine; Cis: cisplatin; GemCis: gemcitabine + cisplatin; Nab: nab-paclitaxel; Pem: pembrolizumab; Dur: durvalumab.

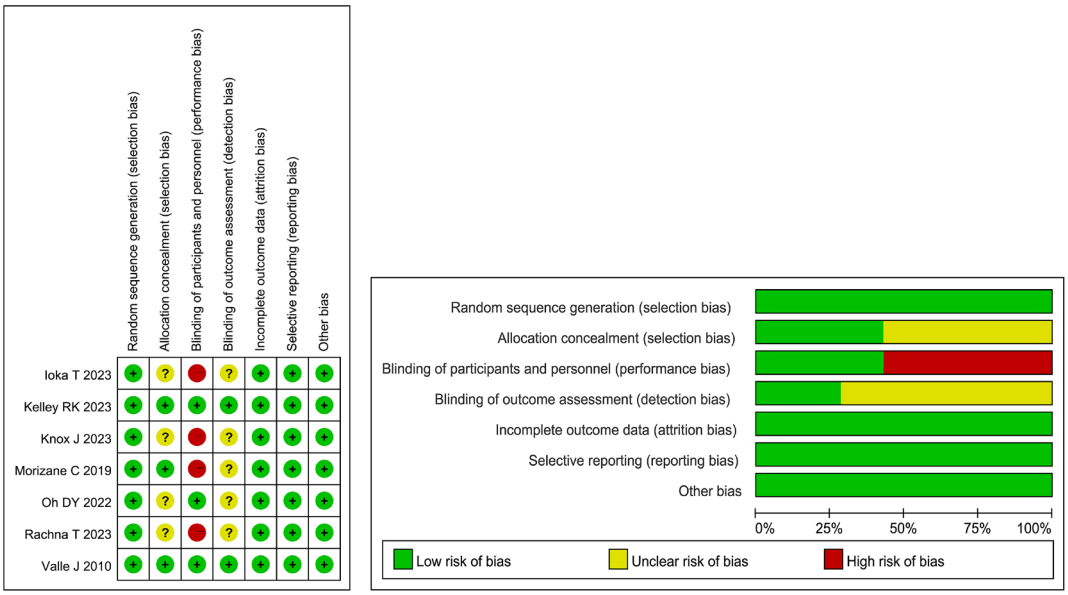

Figure 4. Risk of bias graph for first-line studies: review authors' judgements about each risk of bias item presented as percentages across all included studies.

treatment plans. For this reason, it is critical to compare the benefits of current regimens and increase their efficacy to develop a better treatment plan. Therefore, we ranked first-line systemic therapy regimens for advanced BTC *via* this systematic review and network meta-analysis and found that durvalumab + GemCis is likely to be the best available treatment combination. According to the P score, the durvalumab + GemCis triple therapy has more advantages in terms of evidence certainty and risk of bias, and the Chinese Society of Clinical Oncology guidelines also recommend it as a first-line treatment for advanced BTC level I patients and S-1 + GemCis triple therapy as a first-line treatment for advanced BTC level II patients. Therefore, we prefer durvalumab + GemCis triple therapy as the preferred option. Despite having a low P score, nab-paclitaxel + GemCis was ranked first (8.2 months) solely based on PFS length. The best prescription schedule can be chosen based on the particular circumstances (such as patient location and ethnicity, among other factors) and paired with the economy of care. Simultaneously, treatment approaches such as radiation embolization (*37*) or hepatic artery infusion chemotherapy (*38*) have been developed that combine systemic therapy with local treatments.

Chemotherapy may stimulate the patient's immune response (*39*), and its combination with ICIs may enhance the therapeutic effect. Gemcitabine has been shown to enhance the antitumour immune response (*40,41*). Moreover, the anticancer activity of cisplatin is not solely limited to its ability to inhibit mitosis; rather, it also has important immunomodulatory effects, such as upregulated major histocompatibility complex (MHC) class I expression and a downregulated

immunosuppressive microenvironment (*42*). This provides a reasonable explanation for the results that were obtained in this study.

For advanced BTC, ICIs such as durvalumab have become more crucial in treatment, even though chemotherapy treatment (such as *via* GemCis) is still the primary treatment choice. Moreover, tailored treatments are being quickly developed. Numerous studies have shown that advanced BTCs have a high rate of targetable somatic cell transformation (*43*). Mutations in IDH-1 and IDH-2 (*44*), as well as FGFR rearrangement or fusion (*13*), are two examples of types of transformation. Thus far, several medications have been approved by the Food and Drug Administration (FDA) to treat these BTC changes, including futibatinib (*45*) and pemigatinib (*46*), which target FGFR-2 fusions, and ivosidenib (*47*), which targets IDH-1 mutations; all of these medications are included in the European Association for the Study of the Liver (EASL) and International Liver Cancer Association (ILCA) Clinical Practice Guidelines for the management of intrahepatic cholangiocarcinoma (iCCA) as second-line treatments (*48*).

Due to the fact that most of the information in this study was derived from indirect comparisons, its limitations are related to the nature of the network analysis. Furthermore, the study included only research-quality data rather than specific patient data, which limits its applicability. The ranking probability of the comparative efficacy of various therapies was also estimated *via* the SUCRA curve; however, this method has limitations, and the findings should be evaluated with caution. Despite these drawbacks, this research may contribute to a better understanding of how first-line systemic treatment for advanced BTC is currently evolving.

In conclusion, durvalumab + GemCis is currently the most effective systemic therapy for advanced BTC. Future trials should focus on other possible combinations, as well as sequencing and targeted therapy.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Original Article

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Repeat laparoscopic hepatectomy versus radiofrequency ablation for recurrent hepatocellular carcinoma: A multicenter, propensity score matching analysis

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SUMMARY This study aimed at analyzing and comparing the clinical efficacy and prognosis of repeat laparoscopic hepatectomy (r-LH) and radiofrequency ablation (RFA) in treating recurrent hepatocellular carcinoma (RHCC). Clinicopathological data of RHCC patients who underwent r-LH or RFA as treatment from three medical centers were retrospectively reviewed. Baseline characteristics at the recurrence time after initial hepatectomy and clinical outcomes following treatment of RHCC were compared between the two groups. Using the Kaplan–Meier method, survival curves for the two groups of patients were generated, and the log-rank test was used to compare survival differences. Propensity score matching (PSM) analysis was used to match patients of the r-LH and RFA groups in a 1:1 ratio. A total of 272 patients were enrolled, including 133 patients who underwent r-LH and 139 patients who received RFA. After PSM, 76 patients were matched in each study group. Compared with the r-LH group, the RFA group had shorter hospitalization and fewer postoperative complications. However, the r-LH group had significantly better overall survival (OS) and disease-free survival (DFS) than the RFA group before and after PSM. Subgroup analysis demonstrated that RHCC patients with solitary tumor or those with tumors located near the diaphragm, visceral surface or vessels, had survival benefits from r-LH. When tumor diameter ≤ 5 cm, r-LH appears to be an effective priority to RFA with a significantly higher OS and DFS rate in treating RHCC patients, especially for patients with solitary tumor and those with tumors located near the diaphragm, visceral surface or vessels.

Keywords recurrent hepatocellular carcinoma, survival outcomes, propensity score matching, repeat laparoscopic hepatectomy (r-LH), radiofrequency ablation (RFA)

1. Introduction

Hepatocellular carcinoma (HCC), the third leading cause of cancer-related mortality worldwide (*1,2*), is one of the most common malignant diseases with insidious onset and rapid development. Hepatectomy is one of the first-line treatment modalities for HCC. However, tumor recurrence is common even after initial curative treatment. The 5-year recurrence rate after hepatectomy is 42-52% (*3,4*). Therefore, the management of recurrent hepatocellular carcinoma (RHCC) is pivotal in enhancing patients' long-term prognosis. To date, accounts of salvage treatment options can be considered for patients with RHCC, such as repeat hepatectomy (RH), salvage liver transplantation, transarterial chemoembolization (TACE), stereotactic body radiation therapy(SBRT), chemotherapy, radiotherapy, immunotherapy, and so on (*5*). Hepatectomy, RFA, and liver transplantation are all radical treatments. Due to the shortage of liver donors, hepatectomy and RFA are currently the most commonly considered treatments for RHCC. Medical professionals have always had difficulty deciding which treatment is most reasonable. Nevertheless, limited clinical guidelines and consensus have been proposed for treating RHCC.

RH, including repeat open hepatectomy (r-OH) and repeat laparoscopic hepatectomy (r-LH), has been

proven to be a potentially curative option for patients with RHCC, yielding the best chance at long-term overall survival as well as low morbidity and mortality (*6-8*). With significant developments in laparoscopic instruments and surgical techniques, laparoscopic hepatectomy (LH) has been increasingly performed by experienced surgeons in HCC patients (*9,10*). An increasing number of centers are attempting laparoscopic hepatectomy for RHCC. R-LH may still be beneficial to patients who have intrahepatic recurrences presenting with an adequate functional liver remnant, good liver function, and high performance status (*11*). Though the feasibility of r-LH is restricted by insufficient residual liver volume and technical difficulties owing to expected postoperative adhesion (*12,13*), it is still favored by surgeons for improved perioperative outcomes, postoperative complications, and hospital stays with comparable operation times, overall survival (OS) and recurrence-free survival (RFS) (*14*). For patients, especially those who have undergone laparotomy as their first surgery, LH tends to be a more preferable choice when it comes to the second operation due to the trauma caused by the initial surgery.

In contrast, RFA, as a nonsurgical, less invasive, safe, and repeatable therapeutic approach, has emerged as a new treatment modality and has attracted great interest because of its effectiveness and safety for small HCC (diameter ≤ 5 cm) (*15-17*). It is generally regarded as a safe and effective alternative to partial hepatectomy for early HCC tumors up to 5 cm (*15,18,19*) or intrahepatic recurrences, especially for patients with impaired liver function and when liver transplantation is not indicated (*20-22*). However, RFA has some limitations, including tumor proximity to major vessels, size discrepancies, and limited accessibility of ultrasonography (US) (*23-25*).

In this study, we retrospectively analyzed and compared the efficacy, feasibility, and safety of the two minimally invasive treatments (r-LH and RFA) for patients after the first recurrence of HCC (diameter ≤ 5 cm). The aim of our study was to provide a useful clinical reference and establish a logical treatment algorithm for patients who developed local RHCC following initial hepatectomy for their primary HCC.

2. Patients and Methods

2.1. Patients

From February 2019 to December 2022, a total of 1,027 patients who were admitted to the Eastern Hepatobiliary Surgery Hospital (EHBH), Fujian Provincial Hospital (FPH) and Nanchang University Second Affiliated Hospital with confirmation having recurrent hepatocellular carcinoma by history data and imaging were included in this study. The treatment strategies and surgical methods for individual patients were based on full discussions of multidisciplinary team (MDT) meetings at each medical center. Finally, a total of 272 patients were enrolled, including 133 patients who received r-LH (the r-LH group) and 139 patients who received RFA (the RFA group) (Figure 1). The study protocol was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki and approved by the institutional ethics committee (Approval number: EHBHKY2023-H004-P001).

Clinicopathological variables included sex, age, body mass index (BMI), HBV infection, antiviral therapy, hypertension, diabetes mellitus, routine blood tests, blood biochemical examination, serum alpha-fetoprotein (AFP), Child-Pugh class, cirrhosis, time to recurrence from initial hepatectomy, surgery-related variables, tumor number, size, and location.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the study were as follows: *i*) age ≥ 18 years, *ii*) recurrent hepatocellular carcinoma based on a history of partial hepatectomy for primary hepatocellular carcinoma, and American Association for the Study of Liver Diseases diagnostic criteria for HCC, *iii*) the initial procedure involved performing an R0 resection of primary tumor without visible vascular invasion or extrahepatic distant metastasis, *iv*) no residual disease detected in the first 2 months after initial primary hepatectomy, *v*) computed tomography (CT) or magnetic resonance imaging (MRI) scans at one month after r-LH or RFA confirmed complete tumor clearance at the first reexamination, *vi*) Child-Pugh class A or selected B (score ≤ 7), and *vii*) kidney function and cardiopulmonary function are normal.

We excluded RHCC patients who did not undergo curative hepatectomy as initial treatment or had distant metastasis, incomplete serological, pathological, or follow-up data.

2.3. Diagnosis standard for RHCC

Tumor recurrence was described as the appearance of a new intra- or extrahepatic lesion. Intrahepatic recurrence was defined as a new lesion with arterial contrast enhancement and portal venous washout. The diagnosis of HCC recurrence is mainly determined by the history of previous hepatectomy treatment and the clinical features of the reoccurring tumor by the diagnostic criteria of the National Health Commission (NHSC) or the European Association for the Study of the Liver (EASL) guideline (*1*). Pathological diagnosis of tumor tissue can be obtained by resection or puncture.

2.4. Follow up

All patients received CT or MRI of the liver at one month after r-LH or RFA as the first reexamination

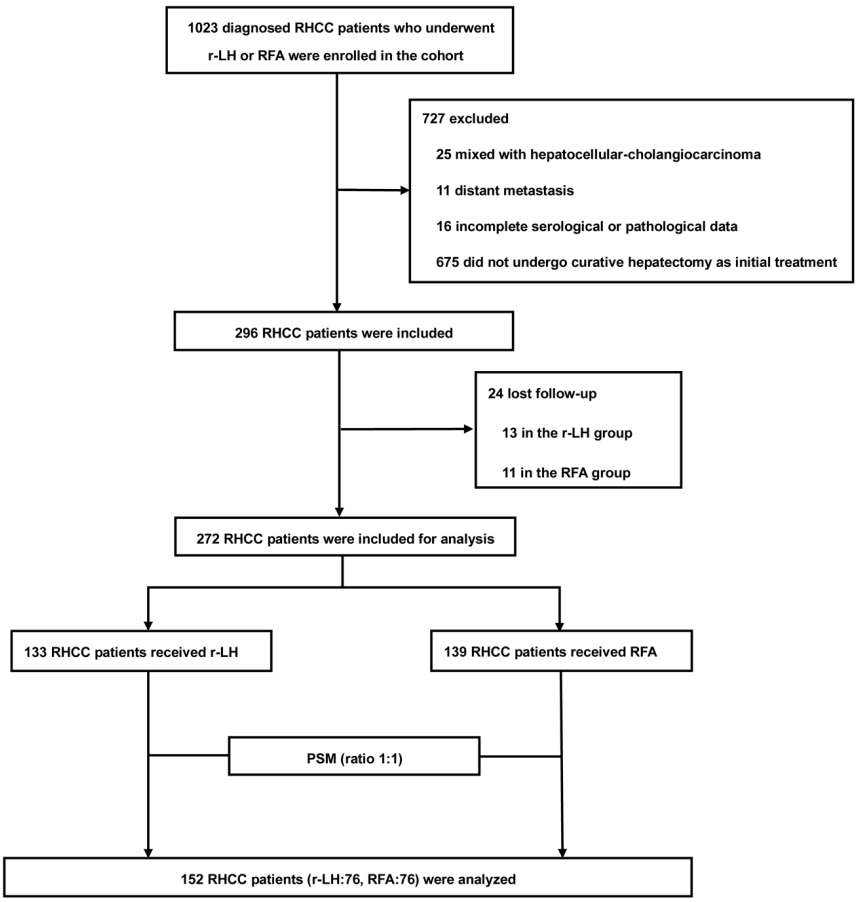

Figure 1. Study flowchart. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; PSM, propensity score matching.

to confirm complete tumor clearance. Thereafter, surveillance for recurrent HCC consisted of measurements of serum alpha-fetoprotein (AFP), liver biochemistry, and ultrasonography, CT scan, or MRI scans of the liver every three months. In case of recurrence of the tumor, follow-up treatment was recommended by the multidisciplinary team. Once tumor recurrence occurred, aggressive management, including RH, TACE, RFA, SBRT, molecular targeted therapy, or immunotherapy, was adopted based on the stage of RHCC and liver function of patients. All patients were followed up regularly until March 2024. The date of tumor recurrence, the date of last follow-up, and the date of death were recorded.

2.5. Study outcomes

The primary outcomes were overall survival (OS), disease-free survival (DFS), and complications. In this study, OS was defined as the time interval between the treatment of RHCC and death from any cause or censoring at the last follow-up, and DFS was defined as the time interval between the treatment of 1st RHCC and 2nd local tumor recurrences in patients. The secondary outcomes included surgery-related parameters, postoperative length of hospital stay and perioperative complications.

2.6. Statistical analyses

For normal distributed continuous variables, means with standard deviation (SD) were shown, and student's *t* test was used to compare differences. For skewed distributed continuous variables, medians with interquartile range (IQR) were expressed, and Mann–Whitney *U* test was applied to compare differences. Categorical data were shown as frequencies and percentages, and compared using Chi-square test or Fisher's exact test as appropriate. The Kaplan–Meier method was used to generate survival curves and the log-rank test was used to compare survival differences. Independent factors associated with DFS and OS were determined using Cox regression models. Hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) were also estimated using Cox regression models. In Cox regression analysis, multivariate analysis was performed with variables yielding $p < 0.05$ in univariate analysis.

Propensity score matching (PSM) analysis was used to minimize the potential confounders and selection

bias and balance the patient baseline characteristics between groups. A 1:1 match between the RFA and r-LH groups was done using the nearest neighbor method with a caliber of 0.2 to prevent poor matching. Variables including sex, age, HBV infection, antiviral therapy, cirrhosis, Child–Pugh class, WBC, platelet, TBIL, ALT, ALB, PT, AFP, time to recurrence from initial hepatectomy, tumor diameter, tumor number and tumor location were matched.

Statistical significance was set as a p value < 0.05 at two-tailed level for all analyses. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA) was utilized for data analyses and visualization in our study.

3. Results

3.1. Baseline characteristics of the patients

The clinicopathological baseline characteristics are shown in Table 1. Among the 272 participants with RHCC, 133 patients underwent r-LH, and 139 patients underwent RFA. 85.7% were males and a total of 80.5% of patients had hepatitis B virus (HBV) infection. Compared with the RFA group, the r-LH group had a lower percentage of cirrhosis (45.1% *vs*. 69.1%, p < 0.001), a higher percentage of WBC > 4×10^9/L (85.0% *vs*. 66.9%, p < 0.001), a higher percentage of TBIL ≤ 17.1μmol/L (79.7% *vs*. 41.7%, p < 0.001), a higher percentage of ALT ≤ 44 (66.9% *vs*. 48.9%, p = 0.003), a lower percentage of PT ≤ 13s (73.7% *vs*. 87.1%, p = 0.005), a lower percentage of AFP ≤ 400ng/mL (76.7% *vs*. 90.6%, p = 0.002), significantly more patients with solitary tumor (85.0% *vs*. 52.5%, p < 0.001). After PSM, all these clinicopathological features were well balanced, and 76 cases in each group were matched and included in the analyses (Table 1).

3.2. Long term outcomes

The Kaplan-Meier method was used to evaluate prognostic value of r-LH and RFA in treatment of patients with RHCC. The median follow-up time of the whole cohort was 51.7 months (95% CI: 47.3-56.0 months), and approximately 40% of the patients (n = 109, 40.1%) died during follow-up. Before PSM, the OS of the r-LH group was significantly longer than that of the RFA group (median OS time, not reached *vs*. 47.7 months; 1-year, 99.2% *vs*. 93.5%; 2-year, 96.2% *vs*. 78.4%; 3 -year, 91.7% *vs*. 62.6%; p < 0.001; Figure 2A). Similarly, the DFS of the r-LH group was markedly longer than that of the RFA group (49.8 months *vs*. 14.2 months; 1-year, 87.2% *vs*. 59.7%; 2-year, 68.4% *vs*. 27.3%; 3-year, 60.9% *vs*. 7.2%; p < 0.001; Figure 2B). The results indicated that the long-term oncological outcomes were significantly better in the r-LH group compared with the RFA group.

After PSM, the long-term prognosis of the r-LH group was also significantly better than the RFA group (for OS: median OS time, not reached *vs*. 58.0 months; 1-year, 100.0% *vs*. 97.4%; 2-year, 97.4% *vs*. 93.4%; 3-year, 93.4% *vs*. 82.9%; p = 0.044; Figure 2C; for DFS: 52.0 months *vs*. 20.8 months; 1-year, 86.8% *vs*. 72.4%; 2-year, 65.8% *vs*. 44.7%; 3-year, 63.2% *vs*. 11.8%; p < 0.001; Figure 2D). The results after PSM still showed better long-term oncological outcomes in the r-LH group compared with the RFA group.

3.3. Independent risk factors associated with OS and DFS

Before PSM, univariate and multivariate analyses demonstrated that WBC < 4×10^9/L, PT > 13s, and RFA treatment were independent risk factors for OS. WBC < 4×10^9/L, multiple tumors, tumors located in other liver segments, and RFA treatment were independent risk factors for DFS (Table 2).

After PSM, as presented in Table 3, univariate and multivariate analyses demonstrated that cirrhosis, WBC < 4×10^9/L, tumors located in other liver segments, and RFA treatment were independent risk factors for OS. Besides, RFA treatment, multiple tumors were independent risk factors for DFS.

3.4. Postoperative complications

As is shown in Table 4, there was no treatment-related mortality in the whole study population. The complication rate in the RFA group was significantly lower than the r-LH group. Before PSM, compared with the r-LH group, there was one patient with bile fistula (0.7% *vs*. 10.5%, p <0.001), one patient with ascites (0.7% *vs*. 21.1%, p < 0.001), two patients with pleural effusion (1.4% *vs*. 15.0%, p <0.001), six patients with fever (4.3% *vs*. 13.5%, p = 0.007), and one patient with needle tract seeding (0.7% *vs*. 0%, p = 0.327) in the RFA group. There were three patients with hepatic failure and nine patients with pulmonary/abdominal infection in the r-LH group. Patients in the RFA group had a shorter median hospital stay and operative time, and a lower transfusion rate compared with the r-LH group (all p < 0.001).

After PSM, minor complications were observed in the RFA group. Compared with the r-LH group, there was one patient with bile fistula (1.6% *vs*. 7.8%, p < 0.001), and three patients with fever (3.9% *vs*. 17.1%, p = 0.008) in the RFA group. There was one patient with hepatic failure, twenty patients with ascites, twelve patients with pleural effusion, and five patients with pulmonary/abdominal infection in the r-LH group. Patients in the RFA group had a shorter median hospital stay (p < 0.001) and operative time (p < 0.001), and a lower transfusion rate (p < 0.001) compared with the r-LH group

Table 1. Baseline clinicopathological characteristics of RHCC patients with treatment of r-LH or RFA before and after PSM analysis

Characteristics	Before PSM			After PSM		
	r-LH (n = 133)	RFA (n = 139)	p value	r-LH (n = 76)	RFA (n = 76)	p value
Age > 60 (%)	60 (45.1%)	47 (33.8%)	0.057	23 (35.9%)	28 (43.8%)	0.367
Sex, male (%)	112 (84.2%)	121 (87.1%)	0.504	65 (85.5%)	62 (81.6%)	0.512
HBV infection (%)	119 (89.5%)	126 (90.6%)	0.746	65 (85.5%)	66 (86.8%)	0.814
Antiviral therapy (%)	105 (78.9%)	114 (82.0%)	0.523	64 (84.2%)	62 (81.6%)	0.667
Cirrhosis (%)	60 (45.1%)	96 (69.1%)	**< 0.001**	42 (55.3%)	47 (61.8%)	0.410
Child–Pugh class						
A	120 (90.2%)	125 (89.9%)	0.935	67 (88.2%)	66 (86.8%)	0.806
B	13 (9.8%)	14 (10.1%)		9 (11.8%)	10 (13.2%)	
WBC($\times 10^9$/L)						
≤ 4	20 (15.0%)	46 (33.1%)	**< 0.001**	14 (18.4%)	11 (14.5%)	0.512
> 4	113 (85.0%)	93 (66.9%)		62 (81.6%)	65 (85.5%)	
Platelet count ($\times 10^9$/L)						
≤ 100	28 (21.1%)	19 (13.7%)	0.107	19 (25.0%)	15 (19.7%)	0.436
> 100	105 (78.9%)	120 (86.3%)		57 (75.0%)	61 (80.3%)	
TBIL (μmol/L)						
≤ 17.1	106 (79.7%)	58 (41.7%)	**< 0.001**	52 (68.4%)	44 (57.9%)	0.179
> 17.1	27 (20.3%)	81 (58.3%)		24 (31.6%)	32 (42.1%)	
ALB (g/L)						
≤ 35	15 (11.3%)	8 (5.8%)	0.102	7 (9.2%)	5 (6.6%)	0.547
> 35	118 (88.7%)	131 (94.2%)		69 (90.8%)	71 (93.4%)	
ALT (U/L)						
≤ 44	89 (66.9%)	68 (48.9%)	**0.003**	52 (68.4%)	44 (57.9%)	0.179
> 44	44 (33.1%)	71 (51.1%)		24 (31.6%)	32 (42.1%)	
PT (s)						
≤ 13	98 (73.7%)	121 (87.1%)	**0.005**	62 (81.6%)	67 (88.2%)	0.258
> 13	35 (26.3%)	18 (12.9)		14 (18.4%)	9 (11.8%)	
AFP (ng/mL)						
≤ 400	102 (76.7%)	126 (90.6%)	**0.002**	60 (78.9%)	66 (86.8%)	0.196
> 400	31 (23.3%)	13 (9.4%)		16 (21.1%)	10 (13.2%)	
Time to recurrence from initial hepatectomy (year)						
≤ 1	101 (75.9%)	103 (74.1%)	0.726	55 (72.4%)	57 (75.0%)	0.713
> 1	32 (24.1%)	36 (25.9%)		21 (27.6%)	19 (25.0%)	
Tumor diameter (cm)						
≤ 3	97 (72.9%)	101 (72.7%)	0.960	58 (76.3%)	57 (75.0%)	0.850
3-5	36 (27.1%)	38 (27.3%)		18 (23.7%)	19 (25.0%)	
Tumor number						
Solitary	113 (85.0%)	73 (52.5%)	**< 0.001**	59 (77.6%)	50 (65.8%)	0.105
Multiple	20 (15.0%)	66 (47.5%)		17 (22.4%)	26 (34.2%)	
Tumor location						
Proximity to diaphragm,visceral surface or vessels	60 (45.1%)	71 (51.1%)	0.325	33 (43.4%)	32 (42.1%)	0.870
Other	73 (54.9%)	68 (48.9%)		43 (56.6%)	44 (57.9%)	

Notes: The symbol bold reflected inside table showed that p-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; PSM, propensity score matching; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

3.5. Subgroup survival analysis in patients associated with tumor number and tumor location

After PSM, post-hoc subgroup analyses showed that among patients with solitary tumor, tumor location with proximity to diaphragm, visceral surface or vessels, patients had significant OS benefits from r-LH than those with RFA (both $p = 0.001$) (Figure 3A, 4A). Furthermore, patients derived significant DFS benefits from r-LH if they had solitary tumor, tumor location with proximity to diaphragm, visceral surface or vessels (both $p < 0.001$) (Figure 3B, 4B). However, no significant differences for OS in patients with multiple tumors, tumors located in other liver segments (both $p > 0.05$) (Figure 3C, 4C) were observed between the r-LH and the RFA group. Besides, no significant differences for DFS in patients with multiple tumors were observed between the r-LH and the RFA group ($p > 0.05$) (Figure 3D).

4. Discussion

HCC is among the most common cancers and is the

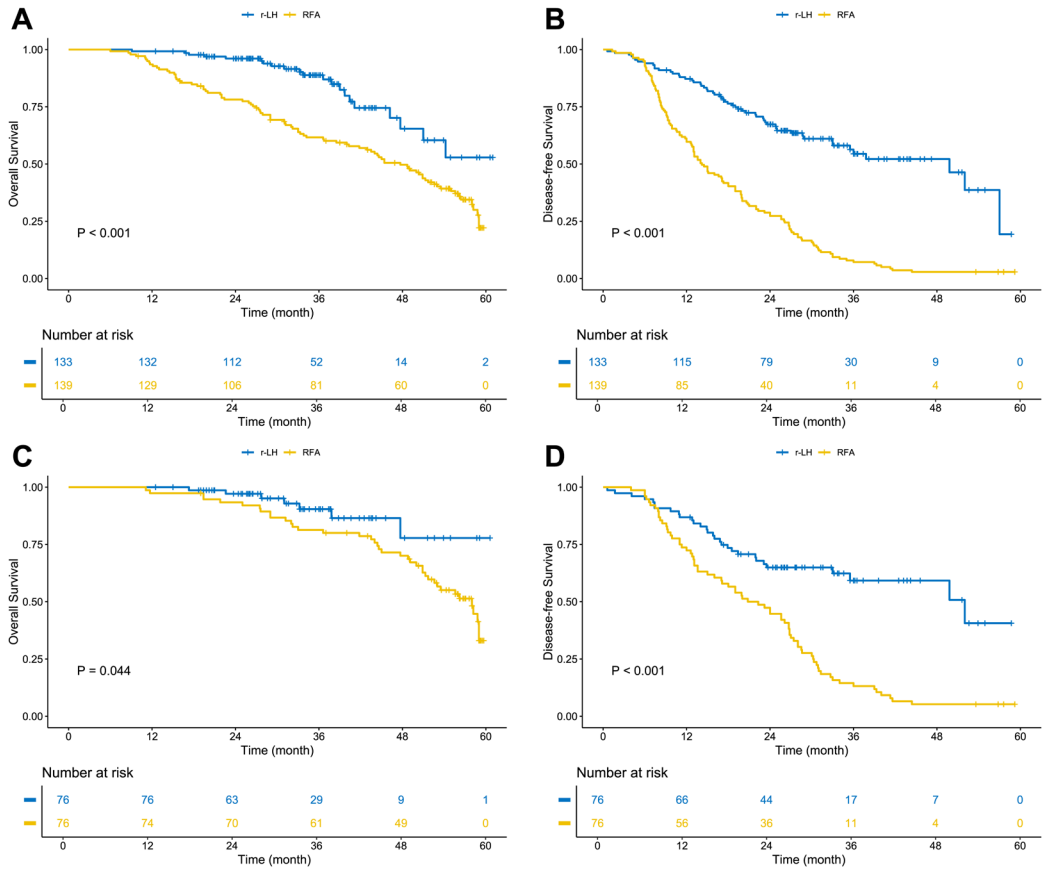

Figure 2. Overall survival (OS) and disease-free survival (DFS) of RHCC patients treated with r-LH or RFA before and after PSM. OS **(A)** and DFS **(B)** of RHCC patients before PSM. OS **(C)** and DFS **(D)** of RHCC patients after PSM. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; PSM, propensity score matching.

leading cause of cancer-related mortality worldwide, with recurrence being a significant clinical challenge after initial surgery. Considering the poor prognosis, RHCC often necessitates complex and multifaceted treatment strategies. Patients who have undergone initial radical hepatectomy face multiple physical and psychological difficulties. In response to RHCC, they often prefer less invasive treatments to avoid exacerbating the distress of their body. R-LH and RFA have emerged as promising therapeutic options, offering minimally invasive approaches with favorable outcomes. In the absence of a structured algorithm for the management of patients with RHCC, r-LH remains the golden choice, while RFA represents a feasible alternative with comparable short- and long-term outcomes. To our knowledge, no high-quality study has examined r-LH vs RFA in the treatment of patients with RHCC. Therefore, in our study, we retrospectively analyzed and compared the long-term oncological outcomes of the patients undergoing either r-LH or RFA, in order to assess the efficacy of these minimally invasive treatments in RHCC patients and determine the optimal treatment approach.

Compared with r-LH, RFA is a highly target-selective thermal treatment technique to conserve non-tumorous liver parenchyma and minimize the degree of surgical insult to the limited liver reserve, preserving the maximum liver remnant (*26*). The characteristics and benefits of less invasiveness and highly-targeted tumor treatment improved the feasibility of patients and repeatability of RFA for RHCC. Compared to surgical intervention, RFA can be safely conducted under conscious sedation, significantly reducing the duration of hospital stay, thereby rendering it a more economically viable option than surgical resection. Given its low complication rates, RFA minimizes perioperative stress, which can even be diminished if performed percutaneously for easily accessible hepatic lesions. These advantages provide the rationale for RFA for RHCC. Nevertheless, studies on primary HCC have revealed that the likelihood of complete ablation diminishes as the tumor diameter increases (*27,28*). In our study, in order to reduce the impact of tumor diameter on prognosis, we selected patients with tumor diameter less than 5cm, and tumor diameter had no effect on OS and DFS benefits between the two subgroups with a diameter of 1-3cm and 3-5cm.

Unlike the surgical approach, the success rate of RFA treatment is influenced by ablative volume, adequate tumor-free margin and necrosis level. High rates of local recurrence with RFA may be attributed to incomplete tumor ablation, satellite tumor nests, and microvascular invasion (*29*). Whether the ablative volume encompasses

Table 2. Univariate and multivariate analysis of overall and disease-free survival for RHCC patients before PSM

Characteristics	HR Comparison	OS						DFS					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	> 60 *vs.* ≤ 60, year	1.19	0.82-1.75	0.362				0.88	0.65-1.18	0.377			
Sex	Female *vs.* Male	0.72	0.44-1.17	0.179				1.01	0.67-1.50	0.980			
HBV infection	Yes *vs.* No	0.89	0.49-1.62	0.697				1.01	0.63-1.60	0.982			
Antiviral therapy	Yes *vs.* No	0.86	0.54-1.36	0.515				0.84	0.59-1.18	0.314			
Cirrhosis	Yes *vs.* No	0.99	0.67-1.46	0.965				1.41	1.05-1.90	**0.021**	1.17	0.86-1.59	0.321
Child–Pugh class	A or B	0.92	0.49-1.71	0.779				0.82	0.51-1.34	0.437			
WBC	> 4 *vs.* ≤ 4, $\times 10^9$/L	2.99	2.00-4.48	**< 0.001**	2.49	1.62-3.83	**< 0.001**	1.92	1.40-2.63	**< 0.001**	1.59	1.13-2.23	**0.008**
Platelet count	> 100 *vs.* ≤ 100, $\times 10^9$/L	1.42	0.82-2.46	0.205				1.14	0.77-1.67	0.515			
TBIL	> 17.1 *vs.* ≤ 17.1, μmol/L	1.26	0.86-1.84	0.235				1.50	1.13-1.99	**0.006**	1.00	0.74-1.35	0.989
ALB	> 35 *vs.* ≤ 35, g/L	1.82	0.84-3.94	0.127				1.45	0.84-2.50	0.182			
ALT	> 44 *vs.* ≤ 44, U/L	0.82	0.56-1.20	0.306				0.64	0.48-0.85	**0.002**	0.75	0.56-1.01	0.058
PT	> 13 *vs.* ≤ 13, s	1.67	1.02-2.71	**0.040**	1.67	1.00-2.78	**0.050**	1.02	0.70-1.47	0.938			
AFP	> 400 *vs.* ≤ 400, ng/mL	0.78	0.44-1.40	0.407	1.20	0.65-2.22	0.561	0.83	0.55-1.25	0.380			
Time to recurrence from initial hepatectomy	> 1 *vs.* ≤ 1, year	0.83	0.55-1.25	0.378				0.94	0.68-1.30	0.701			
Tumor diameter	3-5 *vs.* ≤ 3, cm	0.88	0.58-1.34	0.555				0.93	0.67-1.29	0.662			
Tumor number	Solitary *vs.* multiple	1.88	1.29-2.75	**0.001**	1.45	0.96-2.17	0.077	2.61	1.93-3.52	**< 0.001**	1.93	1.40-2.67	**< 0.001**
Tumor location	Proximity to diaphragm,visceral surface or vessels *vs.* other	0.55	0.38-0.81	**0.002**	0.73	0.49-1.09	0.122	0.63	0.47-0.84	**0.001**	0.69	0.51-0.93	**0.017**
Treatment methods	r-LH *vs.* RFA	0.37	0.23-0.60	**< 0.001**	0.43	0.25-0.73	**0.002**	0.27	0.19-0.36	**< 0.001**	0.34	0.24-0.48	**< 0.001**

Notes: The symbol bold reflected inside table showed that *p*-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

Table 3. Univariate and multivariate analysis of overall and disease-free survival for RHCC patients after PSM

Characteristics	HR Comparison	OS						DFS					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	> 60 *vs.* ≤ 60, year	1.93	1.08-3.46	**0.026**	1.77	0.98-3.17	0.056	1.06	0.71-1.58	0.760			
Sex	Female *vs.* male	0.58	0.30-1.16	0.122				0.85	0.52-1.40	0.517			
HBV infection	Yes *vs.* No	1.06	0.49-2.27	0.891				0.97	0.56-1.67	0.898			
Antiviral therapy	Yes *vs.* No	0.61	0.31-1.21	0.156				0.95	0.57-1.56	0.828			
Cirrhosis	Yes *vs.* No	0.54	0.30-0.96	**0.036**	0.44	0.24-0.80	**0.008**	1.07	0.72-1.59	0.753			
Child–Pugh class	A or B	0.75	2.30-1.90	0.541				0.89	0.49-1.63	0.706			
WBC	> 4 *vs.* ≤ 4, $\times 10^9$/L	2.40	1.17-4.96	**0.018**	2.53	1.19-5.40	**0.016**	1.05	0.62-1.76	0.860			
Platelet count	> 100 *vs.* ≤ 100, $\times 10^9$/L	1.44	0.67-3.08	0.353				1.03	0.65-1.65	0.885			
TBIL	> 17.1 *vs.* ≤ 17.1, μmol/L	0.66	0.35-1.22	0.180				0.81	0.54-1.22	0.320			
ALB	> 35 *vs.* ≤ 35, g/L	2.65	0.64-11.00	0.180				1.27	0.59-2.73	0.547			
ALT	> 44 *vs.* ≤ 44, U/L	0.88	0.49-1.58	0.661				0.77	0.52-1.15	0.203			
PT	> 13 *vs.* ≤ 13, s	1.08	0.38-3.04	0.892				1.22	0.71-2.11	0.476			
AFP	> 400 *vs.* ≤ 400, ng/mL	1.50	0.72-3.11	0.279				0.90	0.53-1.54	0.703			
Time to recurrence from initial hepatectomy	> 1 *vs.* ≤ 1, year	0.79	0.43-1.47	0.458				0.93	0.60-1.45	0.932			
Tumor diameter	3-5 *vs.* ≤ 3, cm	0.91	0.47-1.75	0.771				0.89	0.57-1.40	0.610			
Tumor number	Solitary *vs.* multiple	1.54	0.85-2.78	0.152				1.88	1.23-2.85	**0.003**	1.62	1.06-2.47	**0.025**
Tumor location	Proximity to diaphragm,visceral surface or vessels *vs.* other	0.56	0.31-1.00	**0.050**	0.50	0.27-0.91	**0.024**	0.71	0.48-1.06	0.093			
Treatment methods	r-LH *vs.* RFA	0.44	0.19-1.00	**0.050**	0.39	0.17-0.90	**0.027**	0.33	0.22-0.51	**< 0.001**	0.35	0.23-0.54	**< 0.001**

Notes: The symbol bold reflected inside table showed that *p*-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

Table 4. Intraoperative and postoperative short-term results of RHCC patients who underwent r-LH or RFA before and after PSM

Characteristics	Before PSM			After PSM		
	r-LH (n = 133)	RFA (n = 139)	p value	r-LH (n = 76)	RFA (n = 76)	p value
Surgical variables						
Transfusion(yes)	27 (20.3%)	0 (0%)	< 0.001	14 (18.4%)	0 (0%)	< 0.001
Hospitalization	11 (10-139)	3 (3-59)	< 0.001	11 (10-139)	3 (3-59)	< 0.001
Operative time	140 (110-1809)	20 (20-309)	< 0.001	131 (110-1809)	25 (20-309)	< 0.001
Perioperative complications						
Hepatic failure	3 (2.3%)	0 (0%)	0.075	1 (1.3%)	0 (0%)	0.316
Bile fistula	14 (10.5%)	1 (0.7%)	< 0.001	5 (6.6%)	1 (1.3%)	0.096
Ascites	28 (21.1%)	1 (0.7%)	< 0.001	20 (26.3%)	0 (0%)	< 0.001
Pleural effusion	20 (15.0%)	2 (1.4%)	< 0.001	12 (15.8%)	0 (0%)	< 0.001
Pulmonary/abdominal infection	9 (6.8%)	0 (0%)	0.002	5 (6.6%)	0 (0%)	0.023
Needle tract seeding	0 (0%)	1 (0.7%)	0.327	0 (0%)	1 (1.3%)	0.316
Fever	18 (13.5%)	6 (4.3%)	0.007	13 (17.1%)	3 (3.9%)	0.008

Notes: The symbol bold reflected inside table showed that p-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; PSM, propensity score matching; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation.

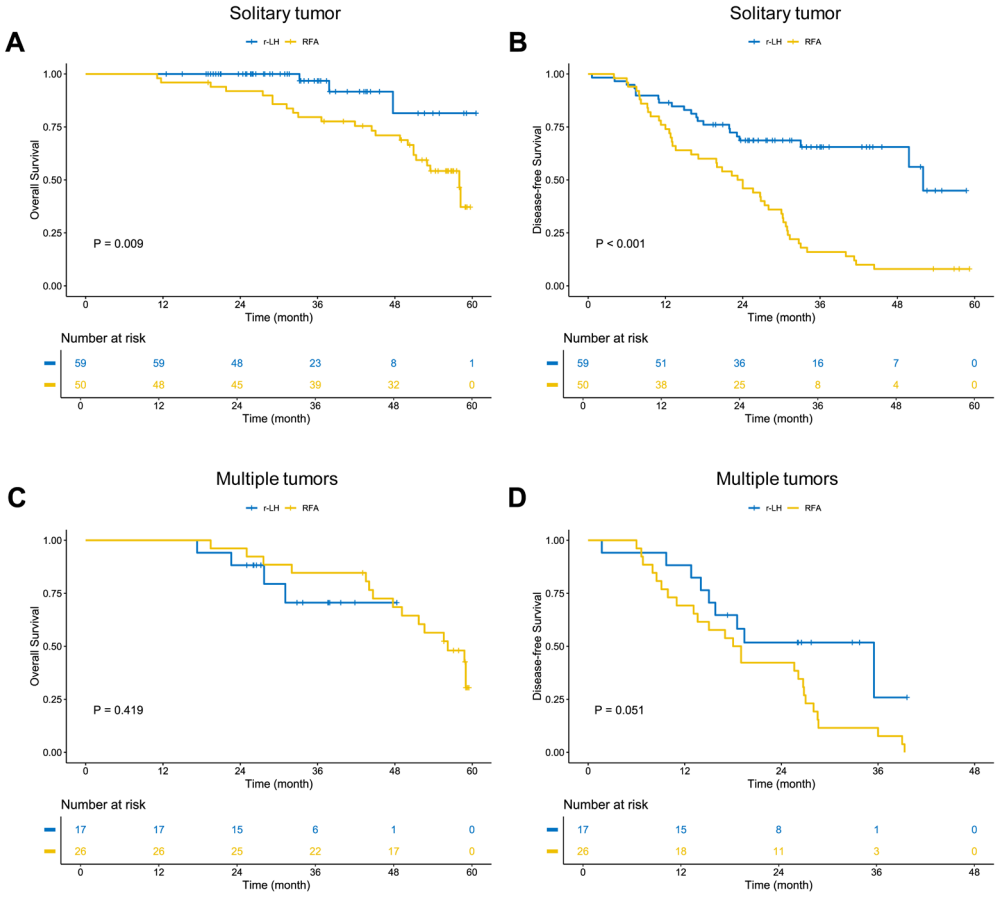

Figure 3. Subgroup analysis OS and DFS based on tumor number. (A, C) Subgroup division according to solitary tumor, and Kaplan-Meier analyses were performed for OS **(A)** and DFS **(C)** associated with r-LH or RFA. **(B, D)** Subgroup division according to other multiple tumors, and Kaplan-Meier analyses were performed for OS **(B)** and DFS **(D)** associated with r-LH or RFA. *Abbreviations*: r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; OS, overall survival; DFS, disease-free survival.

the micrometastasis and microvascular invasion may directly affect the treatment effect of RFA. When performed near a large vessel or liver capsule, it may be associated with potential risk of tumor seeding along the electrode's track and potentially dangerous thermal injury. Generally, it is widely accepted that RFA is

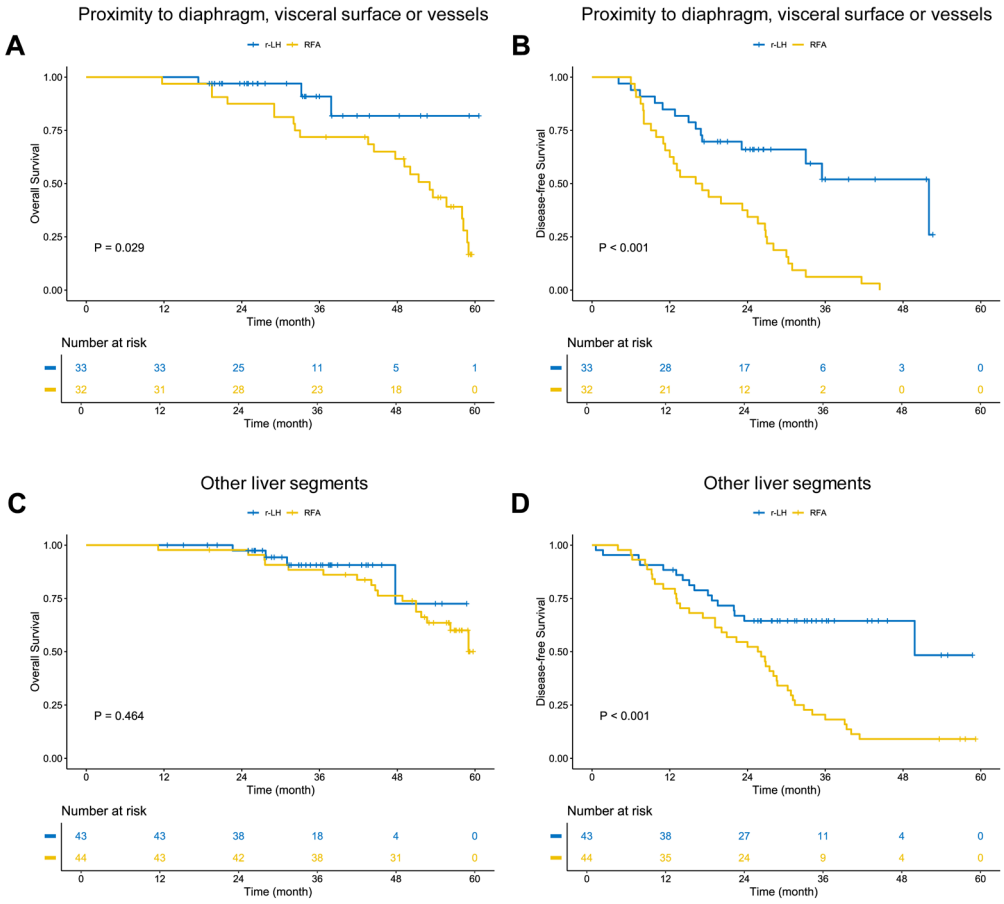

Figure 4. Subgroup analysis OS and DFS based on tumor location. (A, C) Subgroup division according to proximity to diaphragm, visceral surface or vessels, and Kaplan-Meier analyses were performed for OS **(A)** and DFS **(C)** associated with r-LH or RFA. **(B, D)** Subgroup division according to other liver segments, and Kaplan-Meier analyses were performed for OS **(B)** and DFS **(D)** associated with r-LH or RFA. *Abbreviations*: r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; OS, overall survival; DFS, disease-free survival.

technically challenging visualizing the tumor. RFA of tumors in subphrenic (*30*) is associated with higher local recurrence (*31-33*) and risk of major complication rates (*34,35*) due to poor invisibility under US guidance (*30,36*). In addition, when tumors are in proximity to a visceral surface and abutting vital organs such as the heart, stomach or other organs (*37*), they might cause reduction of energy application (*38*). Due to the inconspicuousness of the tumor during ablation, it is somewhat difficult to achieve an adequate ablative margin (*39*). Besides, when the tumor is located next to a major blood vessel (*i.e.*, the portal vein or a major branch of the hepatic vein), the lower blood temperature "cools" the tumor adjacent to the vessel, resulting in an incomplete ablation and "heat-sink" effect (*40,41*). Our study showed that patients derived significant OS benefits from r-LH tumor location with proximity to diaphragm, visceral surface or vessels, while two groups had similar OS benefit if tumors were located in other liver segments. In clinical practice, the local temperature and the ablation time are sometimes insufficient to cause irreversible cell damage in the whole tumor due to the heat sink effect, resulting in a partially viable tumor that subsequently develops into a recurrent lesion after the ablation procedure (*42*). Therefore, tumor location is an important factor affecting the clinical efficacy of RFA for patients with RHCC. Moreover, the achievement of a full ablation rate is influenced not solely by the tumor's location but also by the operator's level of expertise. Therefore, it comes as no surprise that RFA has been frequently reported to have higher recurrence rates than resection for the treatment of HCC (*43*). While RFA was associated with acceptable short and long term outcomes, r-LH was associated with lower re-recurrence and longer overall survival time versus RFA. Several factors could contribute to this phenomenon: Firstly, the rapid heating of the tumor during RFA may lead to the dissemination of tumor cells around the ablation zone or even result in the formation of iatrogenic intra-tumoral shunts, which facilitate the spread of tumor cells to the peripheral regions of the liver (*44*), thereby increasing the risk of tumor recurrence. Secondly, post-RFA, residual microscopic tumor foci may escape detection by post-ablation CT imaging (*45,46*), potentially compromising the assessment of treatment efficacy.

With improvements in liver function assessment,

surgical techniques, perioperative care, and decrease in postoperative morbidity, r-LH, a minimally invasive surgical technique, has gained increased adoption in the management of RHCC. Its advantages include reduced postoperative pain, shorter hospital stays, and faster recovery. R-LH offers the possibility of achieving tumor-free margins while minimizing surgical trauma (*18*), resulting in superior local tumor control. The efficacy of r-LH for RHCC, similar to hepatectomy for primary HCC, remains highly dependent on tumor number and location, patient overall fitness and even more importantly liver function (*7*). In our study, subgroup analyses demonstrated that the two groups had similar OS and DFS benefits if they had multiple tumors, while patients derived significant OS and DFS benefits from r-LH with a solitary tumor. Our results also suggest that the number of tumors affects the efficacy of r-LH in the treatment of RHCC.

R-LH faces greater challenges than the initial hepatectomy due to a range of complexities. Impaired liver function, insufficient liver remnants, postoperative tissue adhesions, and anatomical alterations resulting from previous surgeries all contribute to increased difficulty. The limited visual access and working space, coupled with the presence of adhesions and a deformed liver, increase the risks of severe vital organ injury and uncontrollable bleeding (*47*). Anatomical abnormalities and liver deformation can lead to forced conversion from laparoscopic to open surgery (*48,49*). Despite these challenges, abdominal adhesions offer some advantages in the laparoscopic setting. Tension of the adhesion band can be intensified by gas pneumoperitoneum, making it easier to separate adhesions (*50*). In addition, the small abdominal accesses help preserve portosystemic venous and lymphatic collaterals compared to open surgery, and the targeted laparoscopic vision allows precise surgery without extensive abdominal mobilization, especially in cases of posterior lesions that involve large scars and manipulations of the liver in open surgery (*51,52*). Crucially, preserving the remnant liver function is paramount in r-LH. Excessive resection can exacerbate postoperative liver dysfunction (*53*), necessitating careful surgical planning and execution to minimize such risks. Therefore, a meticulous approach is essential to ensure the safety and success of r-LH.

A comprehensive meta-analysis revealed that repeated surgical resection for RHCC was associated with a notably elevated rate of procedure-related morbidity in comparison to RFA (*54*). Our study also showed procedure-related complication rates were higher in the r-LH group than that in the RFA group. This phenomenon may be attributed to that r-LH is still invasive and carries certain surgical risks. R-LH requires the manipulation of instruments into the abdominal cavity, which may cause some degree of damage to surrounding tissues and organs, such as the gallbladder and intestines, due to the adhesion of the abdominal cavity resulting from the initial surgery, which may increase the incidence of complications. Besides, patients in the RFA group had a shorter median hospital stay and operative time, and a lower transfusion rate compared with the r-LH group before and after PSM.

Several limitations should be acknowledged in this study. First of all, this is a nonrandomized retrospective study with its inherent selection bias and potential confounders. Many patients who are not suitable for surgery were referred for RFA, and this could be a confounding factor. Even if a 1:1 propensity score matching was performed to minimize baseline differences between the r-LH and RFA groups, some other unbalanced variables might still exist. Second, r-LH is still a more complex surgical technique than primary laparoscopic hepatectomy and is gradually being used in the treatment of RHCC. Some patients in the r-LH group have incomplete five-year follow-up data, leading to biased survival outcome comparisons. Third, although the patients included in our study came from three high-volume medical centers, the sample size of the whole cohort was relatively small, which increases the risk of a beta error. Therefore, multi-center and large sample randomized controlled trials should be carried out to further verify our conclusion.

In conclusion, in our study, when tumor diameter ≤ 5 cm, r-LH demonstrated superior OS rate and DFS rate in the treatment of RHCC patients, especially for patients with a solitary tumor and those with tumors located near the diaphragm, visceral surface or vessels. RFA, on the other hand, exhibited a lower postoperative complication rate. Minimally invasive treatment cannot be exchanged at the cost of survival. When survival is the primary goal, r-LH should be the priority for RHCC.

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The APP Score: A simple serum biomarker model to enhance prognostic prediction in hepatocellular carcinoma

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SUMMARY The prognosis for patients with hepatocellular carcinoma (HCC) depends on tumor stage and remnant liver function. However, it often includes tumor morphology, which is usually assessed with imaging studies or pathologic analysis, leading to limited predictive performance. Therefore, the aim of this study was to develop a simple and low-cost prognostic score for HCC based on serum biomarkers in routine clinical practice. A total of 3,100 patients were recruited. The least absolute shrinkage and selector operation (LASSO) algorithm was used to select the significant factors for overall survival. The prognostic score was devised based on multivariate Cox regression of the training cohort. Model performance was assessed by discrimination and calibration. Albumin (ALB), alkaline phosphatase (ALP), and alpha-fetoprotein (AFP) were selected by the LASSO algorithm. The three variables were incorporated into multivariate Cox regression to create the risk score (APP score = 0.390* ln (AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B). The C-index, K-index, and time-dependent AUC of the score displayed significantly better predictive performance than 5 other models and 5 other staging systems. The model was able to stratify patients into three different risk groups. In conclusion, the APP score was developed to estimate survival probability and was used to stratify three strata with significantly different outcomes, outperforming other models in training and validation cohorts as well as different subgroups. This simple and low-cost model could help guide individualized follow-up.

Keywords hepatocellular carcinoma, serum biomarker, overall survival, prognostic score, individualized prediction

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide (*1*). Most patients with HCC have associated chronic liver disease and are usually in the stage of cirrhosis in which development of HCC is one of the main causes of liver-related mortality (*2*). Thus, the prognosis for patients with HCC depends on tumor stage and remnant liver function.

At present, several conventional staging systems such as the American Joint Committee on Cancer (AJCC), China Liver Cancer Staging (CNLC), and Barcelona Clinic Liver Cancer (BCLC) have been proposed for prognostic prediction (*3-5*). However, these systems often include tumor morphology such as tumor size, the number of tumors, and vascular invasion, which are usually assessed with imaging studies or pathologic analysis, leading to limited predictive performance (*6-8*).

Recently, an objective serology-based model known as the BALAD score, which combines bilirubin and albumin with three serum biomarkers (alpha-fetoprotein [AFP], Lens culinaris agglutinin-reactive alpha-fetoprotein [AFP-L3%], and des- gamma-carboxy prothrombin [DCP]), was reported for survival prediction in HCC (*9*). However, it has not been widely used to measure AFP-L3 and DCP, limiting its use in routine clinical practice. The albumin-bilirubin (ALBI) grade also has been used to evaluate liver function in cirrhotic patients and it has a relatively good correlation with prognosis (*10*), but it cannot be used to predict survival in patients with HCC.

Robust molecular subclasses of HCC have also been reported as a result of gene sequencing and/or gene expression profiling over the last decade (*11,12*). However, reliable biomarkers are still needed, and the implementation of tumor subgroups in clinical practice remains challenging due to technical challenges and

cost.

Therefore, the aim of this study was to develop a simple and low-cost prognostic score for HCC that is based on serum biomarkers in routine clinical practice.

2. Patients and Methods

2.1. Patients

Patients with HCC who were seen between January 2012 and December 2018 were identified from a multicenter database. This study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (NO.:2023_045_01) and followed the principles of the Declaration of Helsinki. Informed consent was obtained from each patient for their data to be used for research purposes.

The inclusion criteria included: *i*) HCC diagnosis confirmed by pathology, *ii*) curative resection, *iii*) no macrovascular invasion, *iv*) no distant metastasis, and *v*) Child-Pugh class A or selected B liver function (score ≤ 7). Exclusion criteria were preoperative anticancer therapy, palliative treatment, incomplete data, and loss to follow-up within 2 months of surgery.

2.2. Clinicopathologic variables and follow-up

Blood samples were obtained up to 14 days before surgery for routine laboratory tests for blood cell counts, hepatic and renal function, alpha-fetoprotein (AFP), hepatitis B virus (HBV) and hepatitis C virus (HCV) immunology, and hepatitis B virus deoxyribonucleic acid (HBV-DNA) load. Preoperative imaging studies included chest radiography, abdominal ultrasonography, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen.

Patients were followed up with once every 3 months for the first two years after discharge from the hospital and every 3-6 months in subsequent years. The follow-up program included liver function, AFP level, and abdominal ultrasound. Contrast-enhanced CT or MRI was performed when tumor recurrence was clinically suspected. The end-point of the study was overall survival (OS). OS was defined as the interval between the date of surgery and the date of patient death or last follow-up. The follow-up on October 31, 2023 was censored.

2.3. Statistical analysis

Continuous variables were expressed as the mean (standard deviation, SD) and were compared using the Student *t*-test or as the median (interquartile range, IQR) and compared using the Mann-Whitney *U* test. Categorical variables were expressed as *n* (%) and compared using the chi-square test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

The least absolute shrinkage and selector operation (LASSO) algorithm, with penalty parameter tuning conducted by 10-fold cross-validation, was used to select the significant factors for OS. The prognostic score was created based on multivariate Cox regression of the training cohort.

Model performance was assessed by discrimination and calibration. Model discrimination was measured with Harrell's C-index, Gönen& Heller's K-index, and time-dependent areas under the receiver operating characteristic curve (tdAUC) (*13*). Model calibration was assessed using a calibration curve.

The model was compared to staging systems including Italian Liver Cancer (ITA.LI.CA) (*14*), the 8th American Joint Committee on Cancer Tumor-Node-Metastasis (the 8th AJCC TNM) (*3*), Barcelona Clinic Liver Cancer (BCLC) (*5*), China Liver Cancer Staging (CNLC) (*4*), and Japan Integrated Staging (JIS) (*15*). It was also compared to other models including the albumin-bilirubin (ALBI) grade (*10*), systemic immune-inflammation index (SII) (*16*), neutrophil times the γ-glutamyl transpeptidase to lymphocyte ratio (NrLR) (*17*), prognostic nutritional index (PNI) (*18*), and platelet-to-lymphocyte ratio (PLR) (*19*) in each cohort as well as in different subgroups (Supplemental Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

All statistical tests were 2-tailed and a $p < 0.05$ was considered statistically significant. Statistical analysis was performed with R version 3.5.2 (*http://www.r-project.org/*). The R packages "table1", "rms", "CPE", "timeROC", "stdca", "survminer", and "survival" were used in this study.

3. Results

3.1. Baseline characteristics

A total of 3,100 HCC patients were enrolled and randomly divided into the training (n = 2,100) and validation (n = 1,000) cohorts (Figure 1) in a 2:1 ratio.

The baseline characteristics of patients are shown in Table 1. Of the total, 2,716 (87.6%) patients were positive for viral hepatitis. 2,172 (70.1%) patients were positive for liver cirrhosis. The average size of intrahepatic tumors was 5.64 cm (SD, 3.51 cm). Pathological examinations revealed microvascular invasion in 872 patients (28.2%). There were no significant differences in clinicopathologic features between the training and validation cohorts.

3.2. OS

In this study, the median survival of the entire cohort was 5.31 years (95% CI: 5.23-5.48), with 1-year, 3-year, and 5-year OS rates of 92.1%, 75.7%, and 57.6%,

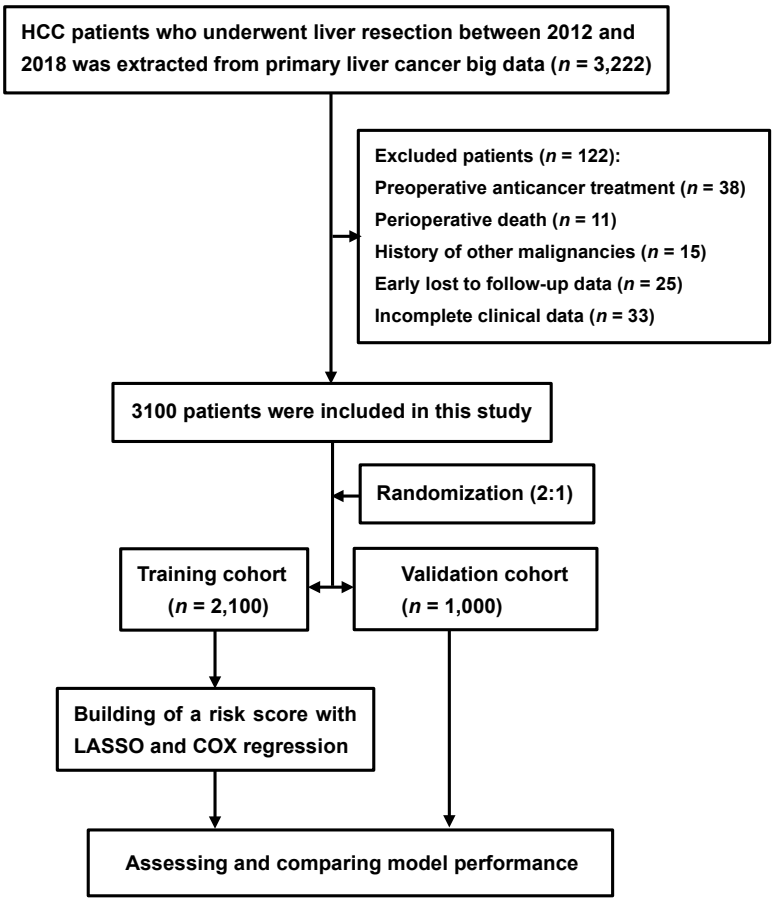

Figure 1. Flow chart for the study design. HCC, hepatocellular carcinoma; LASSO, least absolute shrinkage and selector operation.

Table 1. Baseline characteristics of patients

Variables	Entire cohort (n = 3,100)	Training cohort (n = 2,100)	Validation cohort (n = 1,000)	p-value
Patient factors				
Age [year, Mean (SD)]	51.9 (10.7)	51.8 (10.9)	52.2 (10.5)	0.281
Sex, male/female	2,653/447 (85.6%/14.4%)	1,808/292 (86.1%/13.9%)	845/155 (84.5%/15.5%)	0.260
Etiology				0.750
Hepatitis B	2,716 (87.6%)	1,834 (87.3%)	882 (88.2%)	
Hepatitis C	52 (1.7%)	35 (1.7%)	17 (1.7%)	
Other	332 (10.7%)	231 (11.0%)	101 (10.1%)	
Liver cirrhosis, Absence/Presence	928/2,172 (29.9%/70.1%)	654/1,446 (31.1%/68.9%)	274/726 (27.4%/72.6%)	0.037
Laboratory parameters				
WBC [10^9/L, Mean (SD)]	5.35 (1.71)	5.33 (1.64)	5.40 (1.83)	0.283
Neutrophil [10^9/L, Mean (SD)]	3.18 (1.36)	3.15 (1.28)	3.24 (1.52)	0.724
Lymphocyte [10^9/L, Mean (SD)]	1.63 (0.60)	1.64 (0.59)	1.63 (0.61)	0.283
Monocyte [10^9/L, Mean (SD)]	0.31 (0.13)	0.31 (0.12)	0.31 (0.13)	0.928
Hemoglobin [g/L, Mean (SD)]	143 (15.1)	143 (15.1)	143 (15.1)	0.306
RBC [10^9/L, Mean (SD)]	4.67 (0.52)	4.66 (0.52)	4.67 (0.52)	0.801
PLT [10^9/L, Mean (SD)]	164 (67.2)	164 (66.1)	163 (69.7)	0.557
ALB [g/L, Mean (SD)]	42.4 (3.70)	42.4 (3.73)	42.2 (3.62)	0.261
TBIL [μmol/L, Median (IQR)]	13.2 [10.5, 16.9]	13.3 [10.6, 16.8]	13.2 [10.5, 17.0]	0.904
GGT [IU/L, Median (IQR)]	54.0 [33.0, 96.0]	53.0 [33.0, 94.0]	56.0 [32.8, 100]	0.420
ALP [IU/L, Median (IQR)]	79.0 [65.0, 101]	79.0 [65.0, 100]	79.0 [65.0, 101]	0.329
AFP [ng/mL, Median (IQR)]	48.0 [5.40, 961]	50.0 [5.40, 920]	43.2 [5.30, 1080]	0.753
Tumor factors				
Tumor size [cm, Mean (SD)]	5.64 (3.51)	5.60 (3.53)	5.73 (3.45)	0.326
Tumor number, Solitary/Multiple	3,011/89 (97.1%/2.9%)	2,029/71 (96.6%/3.4%)	982/18 (98.2%/1.8%)	0.019
MVI, Absence/Presence	2,227/873 (71.8%/28.2%)	1,510/590 (71.9%/28.1%)	717/283 (71.7%/28.3%)	0.940

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; MVI, microvascular invasion; SD, standard deviation; IQR, interquartile range.

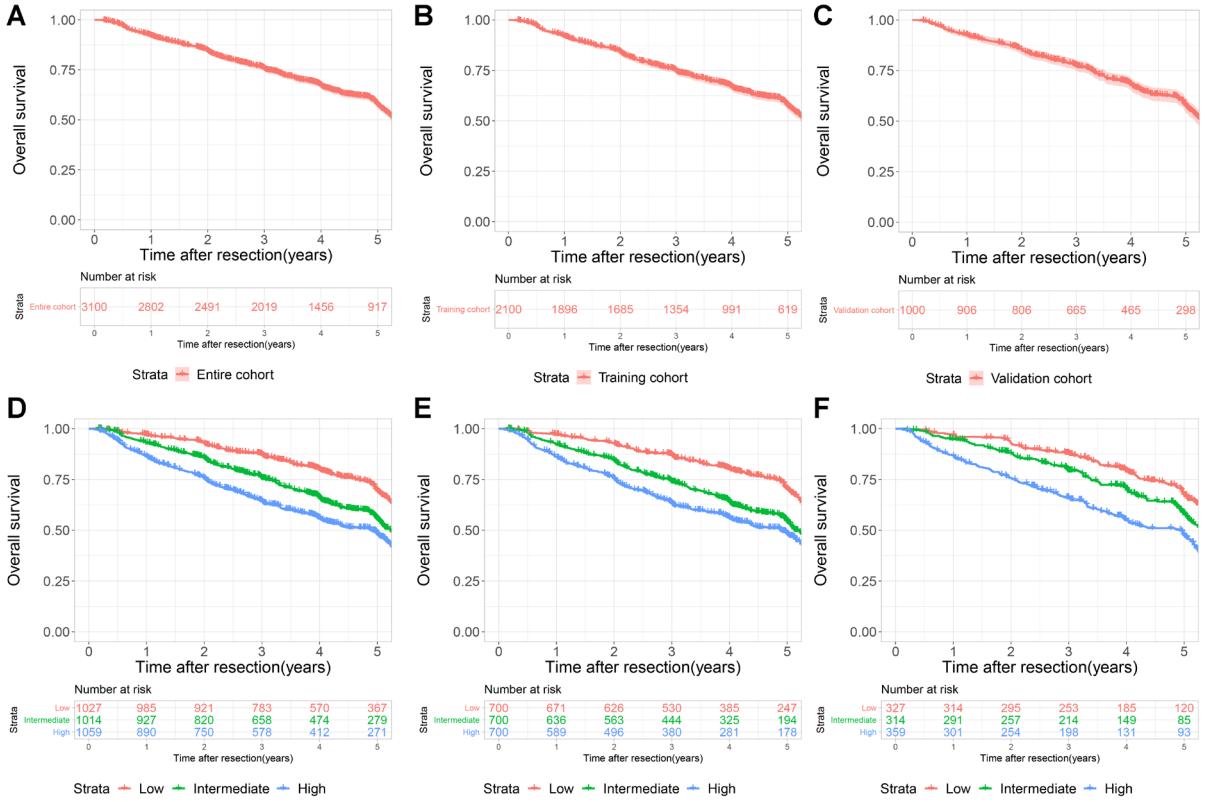

Figure 2. Overall survival. (A) Entire cohort, **(B)** Training cohort, **(C)** Validation cohort, **(D)** Entire cohort stratified by APP score, **(E)** Training cohort stratified by APP score, **(F)** Validation cohort stratified by APP score.

Table 2. Multivariable Cox regression analysis of factors associated with OS in the training cohort

Variables	Multivariable		
	HR (95% CI)	β	*p*-value
ALB, g/L	0.967 (0.950-0.984)	-0.033	< 0.001
ln(ALP)	1.478 (1.311-1.665)	0.390	< 0.001
ln(AFP)	1.065 (1.045-1.086)	0.063	< 0.001
APP score = 0.390* ln(AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B			

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ALB, albumin; ALP, alkaline phosphatase; AFP, alpha-fetoprotein.

respectively (Figure 2A). There were no significant differences in survival between the training and validation cohorts (median OS: 5.31 years [95% CI: 5.23-5.56] *vs*. 5.32 years [95% CI: 5.17-5.58]), (Figure 2B, 2C).

3.3. Devising the APP score

The LASSO algorithm was used to select the significant factors for OS in the training cohort (Supplemental Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). Albumin (ALB), alkaline phosphatase (ALP), and alpha-fetoprotein (AFP) were finally selected. The three variables were incorporated into multivariate Cox regression to create the risk score (**APP score** = 0.390* ln(AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B) (Table 2).

3.4. Risk stratification

Based on the score calculated using the APP score, with 1.26 and 1.57 as the cutoff values (which correspond to the 33rd and 66th centiles), the patients were classified into low-risk, intermediate-risk, and high-risk groups. In the training cohort, the median OS of the low-risk, intermediate-risk, and high-risk groups was 7.55 years (95% CI: 6.24-NA), 5.13 years (95% CI: 5.01-5.44), and 4.88 years (95% CI: 4.33-5.15), respectively. With the low-risk group as a reference, the hazard ratios (HRs) for intermediate-risk and high-risk groups were 1.78 (95% CI: 1.46-2.07; $p < 0.001$) and 2.21 (95% CI: 1.87-2.62; $p < 0.001$), respectively (Table 3). The median OS of the three risk groups in the validation cohort was 8.01 years (95% CI: 5.51-8.72), 5.32 years (95% CI: 5.06-6.00), and 4.96 years (95% CI: 4.01-5.17), respectively. With stratum 1 as a reference, the HRs for strata 2 and 3 were 1.41 (95% CI: 1.10-1.82; $p < 0.001$) and 2.01 (95% CI: 1.59-2.54; $p < 0.001$), respectively (Table 3). Kaplan-Meier analysis showed that the OS rates stratified prognosis among the three risk groups in the training, validation, and entire cohorts ($p < 0.001$) (Figure 2D, 2F).

3.5. Assessment and comparison of model performance

Table 3. Median OS, hazard ratio, and p-value according to each risk group as defined by the APP score

Cohort	Risk group	*n*	Median OS (95% CI), years	Hazard ratio (95% CI)	*p*-value
Training	Low	700	7.55 (6.24, NA)	1	
	Intermediate	700	5.13 (5.01, 5.44)	1.78 (1.46, 2.07)	< 0.001
	High	700	4.88 (4.33, 5.15)	2.21 (1.87, 2.62)	< 0.001
Validation	Low	327	8.01 (5.51, 8.72)	1	
	Intermediate	314	5.32 (5.06, 6.00)	1.41 (1.10, 1.82)	< 0.001
	High	359	4.96 (4.01, 5.17)	2.01 (1.59, 2.54)	< 0.001
Entire	Low	1,027	7.55 (6.24, 8.72)	1	
	Intermediate	1,014	5.23 (5.07, 5.45)	1.62 (1.41, 1.87)	< 0.001
	High	1,059	4.88 (4.33, 5.10)	2.13 (1.86, 2.44)	< 0.001

Abbreviations: OS, overall survival; CI, confidence interval.

Table 4. Comparison of model performance between the APP score and other models in predicting overall survival

Models	Cohort	C-index	K-index	1-yr AUC	3-yr AUC	5-yr AUC
Current model						
APP score	Training	0.619 (0.010)	0.595 (0.009)	0.685 (0.021)	0.660 (0.014)	0.610 (0.016)
	Validation	0.613 (0.015)	0.574 (0.013)	0.670(0.033)	0.659(0.021)	0.581(0.023)
Previous model						
ALBI grade	Training	0.554 (0.011)	0.550 (0.009)	0.541 (0.025)	0.571 (0.015)	0.572 (0.016)
	Validation	0.543 (0.015)	0.531 (0.013)	0.543 (0.032)	0.562 (0.023)	0.544 (0.023)
SII	Training	0.542 (0.011)	0.528 (0.007)	0.599 (0.024)	0.559 (0.015)	0.523 (0.016)
	Validation	0.549 (0.015)	0.526 (0.007)	0.551 (0.037)	0.538 (0.023)	0.552 (0.023)
NrLR	Training	0.584 (0.011)	0.525 (0.003)	0.653 (0.023)	0.611 (0.015)	0.570 (0.018)
	Validation	0.576 (0.015)	0.528 (0.008)	0.619 (0.035)	0.584 (0.023)	0.559 (0.023)
PNI	Training	0.559 (0.011)	0.552 (0.009)	0.554 (0.024)	0.584 (0.015)	0.571 (0.016)
	Validation	0.551 (0.015)	0.535 (0.013)	0.566 (0.032)	0.563 (0.023)	0.552 (0.023)
PLR	Training	0.541 (0.011)	0.527 (0.008)	0.582 (0.024)	0.562 (0.015)	0.539 (0.016)
	Validation	0.544 (0.015)	0.539 (0.010)	0.561 (0.036)	0.546 (0.023)	0.546 (0.023)
Staging system						
ITA.LI.CA	Training	0.606 (0.010)	0.580 (0.008)	0.687 (0.021)	0.636 (0.014)	0.599 (0.015)
	Validation	0.604 (0.015)	0.584 (0.012)	0.667 (0.033)	0.641 (0.021)	0.583 (0.022)
AJCC TNM^{8th}	Training	0.576 (0.009)	0.565 (0.008)	0.600 (0.020)	0.607 (0.013)	0.597 (0.013)
	Validation	0.589 (0.013)	0.575 (0.011)	0.642 (0.031)	0.608 (0.019)	0.592 (0.019)
BCLC	Training	0.512 (0.004)	0.512 (0.004)	0.510 (0.008)	0.517 (0.005)	0.511 (0.006)
	Validation	0.515 (0.005)	0.517 (0.006)	0.520 (0.008)	0.521 (0.007)	0.511 (0.009)
CNLC	Training	0.592 (0.009)	0.579 (0.008)	0.648 (0.018)	0.609 (0.013)	0.602 (0.014)
	Validation	0.578 (0.013)	0.573 (0.011)	0.590 (0.030)	0.606 (0.019)	0.575 (0.020)
JIS	Training	0.572 (0.008)	0.554 (0.007)	0.599 (0.020)	0.602 (0.013)	0.591 (0.012)
	Validation	0.588 (0.013)	0.571 (0.010)	0.639 (0.030)	0.607 (0.019)	0.580 (0.019)

Figures in parentheses are the standard error. *Abbreviations*: AUC, area under the receiver operating characteristic curve; ALBI grade, albumin-bilirubin grade; SII, systemic immune-inflammation index; NrLR, neutrophil times the γ-glutamyl transpeptidase-to-lymphocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; ITA.LI.CA, Italian Liver Cancer; AJCC TNM, American Joint Committee on Cancer Tumor-Node-Metastasis, BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; JIS, Japan integrated staging.

In the training cohort, the C-index of the APP score, ALB, ln(ALP), and ln(AFP) were as follows: 0.619, 0.554, 0.581, and 0.584, respectively. In the validation cohort, the C-index of the APP score, ALB, ln(ALP), and ln(AFP) were as follows: 0.613, 0.539, 0.568, and 0.588, respectively. The C-index, K-index, and time-dependent AUC (1, 3, and 5 years) showed that the APP score was greater than the other 5 staging systems and 5 previous models in training and validation cohorts (Table 4, Figure 3).

Overall, the calibration curves fit well between the predicted and actual outcome in terms of the probability of 1-, 3- and 5-year OS in the training and validation cohorts (Figure 4).

3.6. Subgroup analysis

The APP score was validated in different subgroups of patients according to etiology (non-viral hepatitis and viral hepatitis), liver background (non-liver cirrhosis and liver cirrhosis), tumor size (< 5 cm and ≥ 5 cm), and microvascular invasion (no microvascular invasion and microvascular invasion). The time-dependent AUC for the APP score was still superior to those models, suggesting a consistent performance in these subgroups (Supplemental Figure S2-S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). The APP score was able to stratify patients into the three aforementioned strata across 4 different subgroups, indicating a favorable

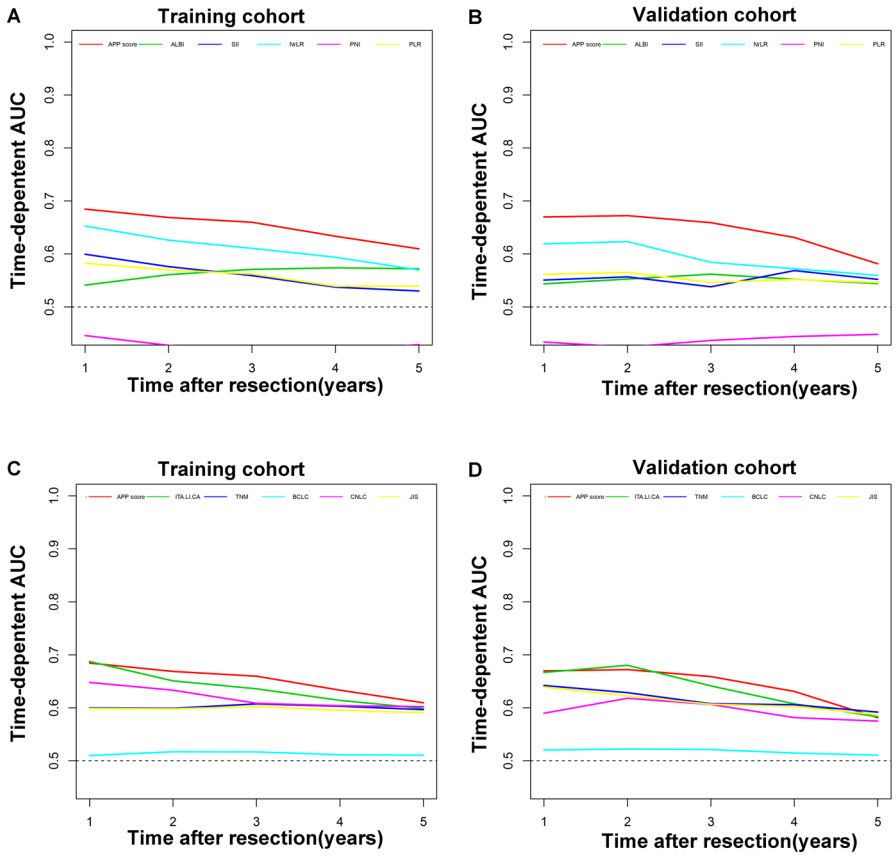

Figure 3. Comparison of the time-dependent AUC between the APP score and other models and staging systems. (A) Between the APP score and previous models in the training cohort, **(B)** Between the APP score and previous models in the validation cohort, **(C)** Between the APP score and staging systems in the training cohort, **(D)** Between the APP score and staging systems in the validation cohort. *Abbreviations*: AUC, area under the receiver operating characteristic curve; ALBI grade, albumin-bilirubin grade; SII, systemic immune-inflammation index; NrLR, neutrophil times the γ-glutamyl transpeptidase-to-lymphocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; ITA.LI.CA, Italian Liver Cancer; AJCC TNM, American Joint Committee on Cancer Tumor-Node-Metastasis; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; JIS, Japan integrated staging.

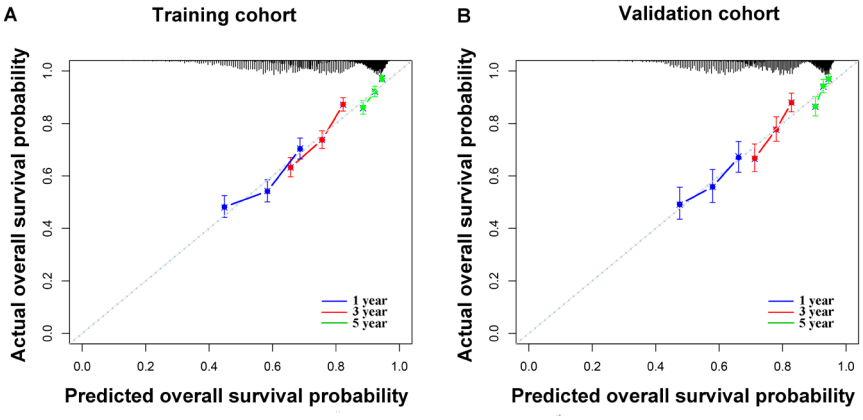

Figure 4. Calibration curves for the APP score. (A) Training cohort, **(B)** Validation cohort.

risk stratification in different populations (Supplemental Figure S6, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

3.7. Risk stratification for recurrence by APP score

In the entire cohort, the 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 74.2%, 53.1%, and 37.6%, respectively (Supplemental Figure S7A, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). Kaplan-Meier analysis revealed no differences in RFS between the training and validation cohorts (Supplemental Figure S7B-C, *https://www.biosciencetrends.com/action/getSupplementalData.*

php?ID=225). Using the cutoff values above, the patients were stratified into low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier analysis showed that the RFS rates stratified prognosis among the three risk groups in the training, validation, and entire cohorts ($p < 0.001$) (Supplemental Figure Figure S7D-F, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

4. Discussion

Based on this large retrospective cohort study, a risk score (APP score) has been developed and verified to predict long-term survival and stratify patients into three risk groups. This model can be calculated from simple, low-cost, and easily obtained blood tests, providing individualized and stratified survival estimates with a favorable level of performance.

The diagnosis of and prognosis for HCC mainly rely on tumor burdens and hepatic function reserve (*20*). Tumor burdens (such as tumor size, tumor number, and vascular invasion) were assessed radiologically or pathologically. However, there might be some variations depending on the method of assessment. Discrepancies exist, and especially with regard to vascular invasion or the number of tumors, so many clinicians suggest using other methods, such as serum biomarkers, as the ideal choice (*21*). The current study used three serum biomarkers (**A**LB, AL**P**, and AF**P**) to create the risk score (APP score). The score is more powerful than other staging systems and models. This simple and low-cost model can help physicians with clinical monitoring.

Liver function is a basic routine blood test to evaluate hepatic function reserve. The APP score is applicable on the basis of two liver function markers (albumin and ALP). Albumin is an important component of the liver. Hypoalbuminemia in HCC is not only induced by impaired liver function due to underlying chronic liver disease but is also associated with a sustained systemic inflammatory reaction (*22*). Albumin has been integrated into several staging systems, including the BCLC and JIS systems (*5,15*).

ALP is widely distributed in human tissues as an enzyme and is metabolized by the liver and finally excreted in the bile (*23*). It is an independent prognostic factor for patients with HCC and is included as one of the parameters in some staging systems such as the CUPI system (*24,25*).

AFP is the most important biomarker used as a screening, diagnostic, and prognostic indicator for HCC (*4*). A higher level of AFP is related to more aggressive tumor features, poorer survival, and poorer treatment responses (*26-29*). A study has shown that patients with AFP-negative HCC have better long-term outcomes than those with AFP-positive HCC (*30*).

There are several limitations to this study. First, selection bias was hard to avoid in a retrospective study. However, this bias has been minimized through use of a large cohort. Second, our model was mainly based on patients with HBV-related HCC who might present with different tumor characteristics than other etiologies such as HCV or alcohol use. However, a subgroup analysis by etiology suggested that our model could be used effectively in patients with etiologies other than HBV. Nonetheless, further external validation is required in different regions.

In summary, the APP score is a novel model based on a simple, low-cost routine blood test and it outperforms other staging systems and previous models. The model stratifies patients into three strata with significantly different outcomes. It provides prognostic information to supplement the tumor staging systems in wide use.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Original Article

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Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: Stratified analysis based on tumor burden score

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SUMMARY The role of laparoscopic liver resection (LLR) for intrahepatic cholangiocarcinoma (ICC) remains debated. This study aimed to evaluate the short- and long-term outcomes of LLR vs. open liver resection (OLR) in ICC stratified by tumor burden score (TBS). ICC patients who underwent LLR or OLR were included from a multicenter database between July 2009 and October 2022. Patients were stratified into two cohorts based on whether the TBS was > 5.3. A 1:3 propensity score matching (PSM) analysis was performed between LLR and OLR in each cohort. Cox regression analysis was used to identify prognostic factors for ICC. A total of 626 patients were included in this study, 304 and 322 patients were classified into the low- and high-TBS groups, respectively. In the low-TBS group, after PSM, LLR was associated with less blood loss, lower CCI, fewer complications and shorter hospital stay (all $p < 0.05$). Kaplan-Meier curves revealed that LLR had better OS ($p = 0.032$). Multivariate Cox regression analysis showed that surgical procedure was an independent prognostic factor for ICC (HR: 0.445; 95% CI: 0.235-0.843; $p = 0.013$). In the high-TBS group, after PSM, LLR were associated with reduced blood loss, lower CCI, fewer complications and shorter hospital stay (all $p < 0.05$), while OS ($p = 0.98$) and DFS ($p = 0.24$) were similar between the two groups. TBS is an important prognostic factor for ICC. LLR is a safe and feasible option for ICC and leads to faster postoperative recovery. LLR can offer ICC a comparable and even better long-term prognosis than OLR.

Keywords tumor burden score, intrahepatic cholangiocarcinoma, laparoscopic liver resection, open liver resection, propensity score matching

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), which arises from the epithelial cells of the intrahepatic bile duct, is the second most common primary liver cancer, accounting for up to 20% of all liver malignancies and 3% of gastrointestinal malignancies (*1,2*). The incidence of ICC has consistently increased over the past four decades (*3*). In the USA, this rate is increasing, with an annual percentage change of 2.3%, from 0.44 to 1.18 cases per 100,000 people between 1973 and 2012 (*3*). Surgical resection remains the first-line treatment strategy for ICC, which could be the only potential cure and provide a 5-year overall survival (OS) ranging from 20% to 35% (*4*).

Recently, with the development of laparoscopic instruments and progress in surgical experience, laparoscopic liver resection (LLR) has been widely performed for the treatment of liver disease (*5,6*). Compared with open liver resection (OLR), LLR is associated with decreased tissue damage, less blood loss, lower occurrence of complications and a shorter hospital stay (*7,8*). Although ICC is not a contraindication for LLR, due to concerns of inadequate resection margins, uncontrollable hemorrhage and failure of lymph node dissection (LND), few reports on this topic are available (*9*). Moreover, previous studies have focused mainly on the resection of small solitary ICCs, and data related to the application of LLR for large or multiple ICCs are scarce (*10*). The feasibility and safety of LLR for varying sizes or numbers of ICCs has yet to be fully elucidated. Consequently, selecting the optimal surgical strategy for

ICC remains a troublesome problem.

Tumor Burden Score (TBS), introduced in 2017, serves as a prognostic tool derived from tumor size and number and is primarily intended for colorectal liver metastases (CRLM) (*11*). Recently, TBS has been applied to stratify the prognosis of several different cancers in the liver, including hepatocellular carcinoma, ICC and CRLM (*11-14*). As such, the objective of this study was to compare the clinical characteristics of different TBS groups among patients who underwent curative liver resection for ICC using a large, multicenter cohort of patients. In addition, we sought to compare the short- and long-term outcomes between LLR and OLR for ICC treatment in different TBS groups in a case-matched analysis *via* propensity score matching (PSM) and to identify perioperative variables that influence ICC prognosis, which could provide clinicians with insights into surgical options and improve the prognosis of ICC patients.

2. Materials and Methods

2.1. Patient selection

Patients who underwent curative-intent liver resection between June 2009 and October 2022 at Shandong Provincial Hospital Affiliated to Shandong First Medical University, West China Hospital of Sichuan University and The First Affiliated Hospital of Zhengzhou University were enrolled. This study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University, West China Hospital of Sichuan University and The First Affiliated Hospital of Zhengzhou University, and informed consent was obtained from all patients.

Patients who met the following criteria were selected: *i*) ICC diagnosed based on postoperative histopathology; *ii*) good liver function, Child–Pugh class A/B (score ≤ 7); and *iii*) curative hepatectomy. The exclusion criteria were as follows: *i*) palliative hepatectomy (R1 or R2); *ii*) patients who were converted to laparotomy after endoscopic surgery; *iii*) patients with extrahepatic metastasis or recurrent liver cancer; *iv*) patients who had received neoadjuvant therapy; and *v*) patients with incomplete follow-up data.

2.2. TBS definition and TBS grade evaluation

Preoperative imaging reports were collected for each enrolled patient to obtain accurate maximum tumor diameter and tumor number data. TBS is defined as the distance of two variables, the maximum tumor diameter (x-axis) and the tumor number (y-axis), from the origin of the Cartesian plane. The formula applies Pythagoras 'theorem: TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2. X-tile software was used to determine the optimal cut-off value for TBS (5.30 units) (*15*). Patients were subsequently divided into high- and low-TBS groups according to the optimal cut-off value.

2.3. Data collection and liver resection

All patient information, including demographic details, preoperative laboratory data, surgery-related parameters and postoperative outcomes, was reviewed and retrieved from hospital electronic medical records. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as follows: NLR = absolute neutrophil count/absolute lymphocyte count; PLR = absolute platelet count/absolute lymphocyte count (*16,17*). Surgical complications were evaluated according to the Clavien–Dindo (CDc) classification system and comprehensive complication index (CCI) (*18,19*). Tumor staging was determined according to the American Joint Committee on Cancer (AJCC) 8th Edition staging system. All procedures were performed by experienced hepatobiliary surgeons. Before performing surgery, patients and their families must understand the pros and cons of LLR and OLR; we discuss the risks of surgery with them, and finally make decisions based on the patient's own situation.

2.4. Follow-up

Patients need regular follow-up after surgery, first in the first month after discharge to the outpatient clinic for the first re-examination; every three months for the next two years; and from the third year to the hospital every six months for re-examination, until death or loss to follow-up. The examinations included liver function tests, serum alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and enhanced abdominal CT or magnetic resonance imaging (MRI) examinations. Recurrence was defined as local recurrence or distant metastasis detected by dynamic contrast-enhanced CT or MRI. OS was calculated from the time of liver resection to the last follow-up or death from any cause. Disease-free survival (DFS) was calculated from the time of hepatectomy to the last follow-up or tumor recurrence. The follow-up data were collected as of 31 August 2023.

2.5. Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney *U* test. Categorical variables are expressed as numbers (percentages) and were analyzed *via* the chi-square test or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method and compared *via* the log-rank test. The patients were categorized into a high TBS group (n = 322) and a low TBS group (n = 304) based on an optimal TBS cut-

off value of 5.30. To mitigate discrepancies in baseline characteristics between the LLR and OLR groups, a 1:3 propensity score matching was conducted utilizing nearest neighbor matching within both the high and low TBS groups. The covariates employed for achieving balance included all baseline variables, excluding surgical outcomes, with a caliper radius established at a standard deviation of 0.02 to ensure adequate matching quality. After the matching, continuous variables were compared using the Mann-Whitney *U* test, while categorical variables were assessed through the chi-square test or Fisher's exact test to identify any residual imbalances. Univariate and multivariate Cox proportional hazards models were used to identify prognostic factors associated with OS. In univariate analyses, variables with $p < 0.1$ were considered worthy of inclusion in multivariate analyses. The optimal cut-off value of TBS was calculated *via* X-tile software (3.6.1). All other statistical analyses were performed using SPSS software (27.0) and R (4.4.0). All tests were two-tailed, and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the entire study population

The flow chart of this study is shown in Figure 1. A total of 947 liver resections for ICC were conducted during the study period, of which 626 patients who underwent curative liver resection and met the inclusion criteria were enrolled. The baseline characteristics of the 626 patients are shown in Table 1. The median age was 59.0 years, with 339 male patients (54.2%). A total of 243 (38.8%) patients received LND, while 127 (20.3%) patients underwent LLR. The median diameter of the largest lesion was 5.3 cm, while multiple tumors were present in 89 (14.2%) of the patients; consequently, the median TBS was 5.49.

The optimal cut-off value of the TBS for OS was determined to be 5.30 according to X-tile analysis (Supplemental Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=230*). Accordingly, 304 patients (48.6%) and 322 patients (51.4%) were classified into the low- and high-TBS groups, respectively. Patients with high TBS disease more often had poorer oncologic features and worse preoperative laboratory tests. The KM analysis revealed that patients in the high-TBS group had a significantly poorer prognosis than those in the low-TBS group ($p <$ 0.01).

3.2. Patient characteristics between different surgical procedures in the low- and high-TBS groups

Table 2 presents the baseline characteristics of the participants in the low-TBS cohort. A total of 68 (22.4%) patients underwent LLR. Before PSM, there were notable differences between the LLR and OLR groups in body mass index (BMI, 23.31 *vs*. 24.34 kg/m^2; $p = 0.020$), platelet (PLT, 176.00 *vs.* 198.00*10^9/L; $p = 0.044$), PLR (107.50 *vs.* 124.81; $p = 0.046$), white blood cell (WBC, 5.90 *vs.* 5.46*10^9/L; $p = 0.019$), neutrophil (NE, 3.69 *vs.* 3.23*10^9/L; $p = 0.019$), aspartate aminotransferase (AST, 27.00 *vs.* 25.00u/L; $p = 0.042$), and CA199 (50.77 *vs.* 28.03 u/mL; $p = 0.003$). Notably, disparities in nerve invasion ($p = 0.048$), lymphatic metastasis ($p = 0.009$), Adjuvant therapy ($p = 0.020$) and TNM stage ($p < 0.001$) were noted between the two groups. After PSM, the OLR group consisted of 93 patients, while the LLR group included 47 patients, with a more balanced distribution of characteristics between the two groups.

The baseline characteristics of patients in the high-TBS cohort are presented in Table 3. The LLR group consisted of 59 (18.3%) ICC patients. Before PSM, there were notable differences between the LLR and OLR groups in BMI (22.84 *vs*. 24.91 kg/m^2; $p < 0.001$), PLT (190.00 *vs*. 233.00*10^9/L; $p < 0.001$), total bilirubin (TB, 13.60 *vs.* 11.50 μmol/L; $p = 0.004$), alanine aminotransferase (ALT, 25.00 *vs.* 19.00 U/L; $p = 0.005$), AST (31.00 *vs*.25.00 U/L; $p < 0.001$), alkaline phosphatase (ALP, 128.00 *vs*. 99.00 U/L; $p < 0.001$), GGT (88.00 *vs.* 51.00 U/L; $p < 0.001$), AFP (3.50 *vs*. 2.70 ng/mL; $p = 0.018$), lymphatic metastasis (24.7 *vs.*

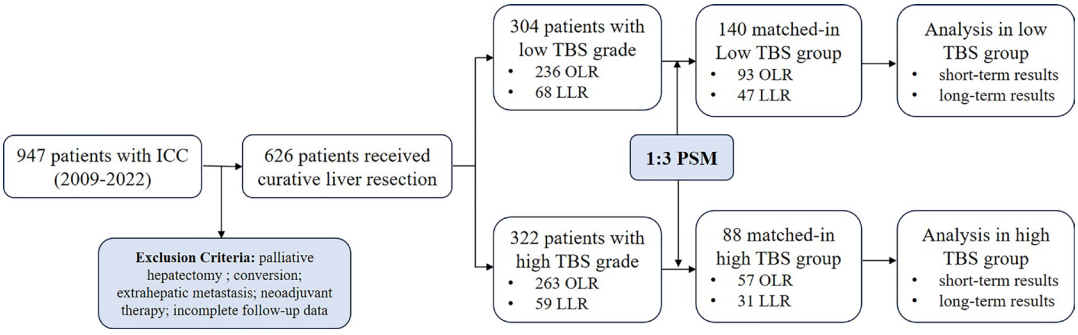

Figure 1. Flow chart of this study showing the selection process of ICC patients who underwent LLR or OLR. ICC intrahepatic cholangiocarcinoma, LLR laparoscopic liver resection, OLR open liver resection, PSM propensity score matching. Because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3.

Table 1. The baseline characteristics and surgical outcomes of ICC patients in the total cohort, low TBS cohort, and high TBS cohort

Variables	The total cohort (*n* = 626)	Low TBS cohort (*n* = 304)	High TBS cohort (*n* = 322)	*p* value
Age, median (IQR), years	59.00 (51.00-65.00)	58.00 (50.00-65.00)	59.00 (51.00-65.00)	0.464
Gender				0.483
Female, *n* (%)	287 (45.8)	135 (44.4)	152 (47.2)	
Male, *n* (%)	339 (54.2)	169 (55.6)	170 (52.8)	
Short stature, median (IQR), m	1.63 (1.57-1.69)	1.63 (1.58-1.70)	1.63 (1.57-1.69)	0.192
Weight, median (IQR), Kg	61.00 (54.14-70.00)	62.28 (54.11-71.00)	60.14 (54.38-68.03)	0.138
BMI, median (IQR), kg/m^2	23.31 (20.96-25.75)	23.67 (20.85-25.93)	23.06 (21.15-25.68)	0.466
Hypertension, *n* (%)	151(24.1)	79 (26.0)	72 (22.4)	0.289
Diabetes, *n* (%)	60 (9.6)	27 (8.9)	33 (10.2)	0.561
Alcohol, *n* (%)	139 (22.2)	62 (20.4)	77 (23.9)	0.290
HBV, *n* (%)	177 (28.3)	90 (29.6)	87 (27.0)	0.473
HCV, *n* (%)	4 (0.6)	4 (1.3)	-	**0.039**
WBC, median (IQR), 10^9/L	6.40 (5.17-7.73)	5.83 (4.78-7.06)	6.96 (5.65-8.18)	**< 0.001**
NE, median (IQR), 10^9/L	4.07 (3.13-5.34)	3.57 (2.81-4.58)	4.55 (3.64-5.77)	**< 0.001**
Lym, median (IQR), 10^9/L	1.53 (1.20-1.89)	1.55 (1.20-1.97)	1.53 (1.21-1.85)	0.426
NLR, median (IQR), %	2.64 (1.86-3.69)	2.2 9(1.62-3.18)	2.98 (2.20-4.28)	**< 0.001**
PLT, median (IQR), 10^9/L	190.00 (138.00-239.50)	182.00 (131.00-230.00)	196.00 (148.75-250.00)	**0.004**
PLR, median (IQR), %	121.28 (88.41-167.12)	110.50 (85.71-151.72)	131.06 (93.57-180.96)	**0.001**
PT, median (IQR), s	1.02 (0.97-1.08)	1.02 (0.97-1.07)	1.01 (0.96-1.08)	0.640
INR, median (IQR), %	11.90 (11.20-12.70)	11.80 (11.20-12.60)	11.90 (11.20-12.83)	0.346
TB, median (IQR), μmol/L	14.40 (10.90-19.20)	15.10 (11.70-20.33)	13.05 (10.25-18.23)	**<0.001**
ALT, median (IQR), U/L	24.00 (16.00-39.00)	25.00 (16.00-41.00)	24.00 (16.00-38.00)	0.175
AST, median (IQR), U/L	28.00 (22.00-39.00)	27.00 (21.00-36.00)	30.00 (24.00-40.25)	**0.012**
ALP, median (IQR), U/L	108.00 (84.50-165.00)	96.00 (77.00-140.00)	121.50 (94.75-181.25)	**< 0.001**
GGT, median (IQR), U/L	65.00 (34.00-154.00)	54.00 (26.00-134.00)	74.00 (43.00-165.50)	**< 0.001**
AFP, median (IQR), ng/mL	3.03 (1.98-5.34)	2.83 (1.90-4.50)	3.36 (2.07-6.09)	**0.002**
CA199, median (IQR), U/mL	58.50 (17.02-558.70)	47.11 (15.70-262.70)	93.15 (20.51-834.03)	**0.001**
CA125, median (IQR), U/ml	18.80 (9.51-61.87)	15.28 (8.65-39.71)	26.55 (10.79-87.44)	**< 0.001**
CEA, median (IQR), ng/mL	2.86 (1.60-5.91)	2.78 (1.54-4.80)	3.02 (1.60-8.06)	0.160
Child–Pugh, *n* (%)				0.917
A	580 (92.7)	282 (92.8)	298 (92.5)	
B	46 (7.3)	22 (7.2)	24 (7.5)	
Nerve invasion, *n* (%)	103 (16.5)	72 (23.7)	31 (9.6)	**< 0.001**
Differentiation, *n* (%)				0.288
Poor	339 (54.2)	158(52.0)	181 (56.2)	
Moderate / Well	287 (45.8)	146(48.0)	141 (43.8)	
Satellite nodules, *n* (%)	75 (12.0)	22 (7.2)	53 (16.5)	**< 0.001**
Lymphatic metastasis, *n* (%)	123 (19.6)	55 (18.1)	68 (21.1)	0.341
Capsular invasion, *n* (%)	326 (52.1)	132 (43.4)	194 (60.2)	**< 0.001**
Maximum tumor size (IQR), cm	5.30 (3.70-7.20)	3.55 (3.00-4.50)	7.00 (6.00-9.00)	**< 0.001**
Multiple tumors, *n* (%)	89 (14.2)	28 (9.2)	61 (18.9)	**< 0.001**
TNM, *n* (%)				**0.008**
I/II	322 (51.4)	173 (56.9)	149 (46.3)	
III/IV	304 (48.6)	131 (43.1)	173 (53.7)	
Operation time (IQR), min	240.00 (180.00-305.00)	210.00 (170.00-278.75)	255.00 (180.00-320.00)	**0.008**
Blood loss (IQR), ml	200.00 (20.00-400.00)	100.00 (20.00-200.00)	300.00 (100.00-400.00)	**< 0.001**
CCI (IQR)	8.70 (8.70-22.60)	8.70 (8.70-22.60)	8.70 (8.70-22.60)	0.833
CD, *n* (%)	82 (13.1)	40 (13.2)	42 (13.0)	0.966
Lymph node dissection, *n* (%)	243 (38.8)	105 (34.5)	138 (42.9)	**0.033**
Length of hospital stay (IQR), d	12.00 (10.00-16.00)	12.00 (9.75-16.00)	13.00 (11.00-17.00)	0.141
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	4.00 (3.00-5.25)	4.00 (3.00-6.00)	0.759
Postoperative discharge time (IQR), d	8.00 (6.00-11.00)	8.00 (6.00-10.00)	9.00 (7.00-11.00)	0.060
Surgical approach, *n* (%)				0.208
LLR	127 (20.3)	68 (22.4)	59 (18.3)	
OLR	499 (79.7)	236 (77.6)	263 (81.7)	
Adjuvant therapy, *n* (%)	200 (31.9)	93 (30.6)	107 (33.2)	0.479

Data are presented as *n* (%) or median (IQR); Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III; IQR, interquartile range.

Table 2. The baseline characteristics of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 304)		p value	After PSM (n =140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Age, median (IQR), years	58.00 (50.00-65.00)	59.00 (50.25-66.00)	0.436	60.00 (51.50-67.50)	58.00 (50.0-66.00)	0.400
Gender			0.543			0.770
Female, n (%)	107 (45.3)	28 (41.2)		40 (43.0)	19 (40.4)	
Male, n (%)	129 (54.7)	40 (58.8)		53 (57.0)	28 (59.6)	
Short stature, median (IQR), m	1.63 (1.58-1.70)	1.63 (1.58-1.70)	0.775	1.65 (1.58-1.70)	1.63 (1.58-1.68)	0.757
Weight, median (IQR), Kg	61.00 (53.00-70.00)	64.00 (58.00-74.00)	**0.049**	61.19 (56.00-73.25)	63.00 (56.0-71.00)	0.522
BMI, median (IQR), kg/m^2	23.31 (20.76-25.75)	24.34 (21.93-26.35)	**0.020**	23.36 (20.76-25.92)	24.22 (21.9-25.97)	0.302
Hypertension, n (%)	58 (24.6)	21 (30.9)	0.296	24 (25.8)	14 (29.8)	0.617
Diabetes, n (%)	21 (8.9)	6 (8.8)	0.985	10 (10.8)	5 (10.6)	0.984
Alcohol, n (%)	43 (18.2)	19 (27.9)	0.080	17 (18.3)	13 (27.7)	0.201
HBV, n (%)	72 (30.5)	18 (26.5)	0.520	35 (37.6)	13 (27.7)	0.240
HCV, n (%)	3 (1.3)	1 (1.5)	0.899	0 (0)	0 (0)	-
WBC, median (IQR), 10^9/L	5.90 (4.88-7.15)	5.46 (3.91-6.75)	**0.019**	5.80 (4.76-6.79)	5.91 (4.72-7.16)	0.938
NE, median (IQR), 10^9/L	3.69 (2.88-4.69)	3.23 (2.25-4.32)	**0.019**	3.50 (2.71-4.30)	3.53 (2.48-4.47)	0.714
Lym, median (IQR), 10^9/L	1.54 (1.20-1.97)	1.58 (1.15-1.93)	0.591	1.57 (1.26-2.00)	1.65 (1.27-2.00)	0.817
NLR, median (IQR), %	2.29 (1.66-3.22)	2.27 (1.52-2.89)	0.156	2.20 (1.55-2.78)	2.10 (1.31-2.85)	0.616
PLT, median (IQR), 10^9/L	176.00 (128.00-223.00)	198.00 (147.00-238.00)	**0.044**	183.00 (128.43-234.00)	198.00 (138.00-236.00)	0.443
PLR, median (IQR), %	107.50 (82.69-147.72)	124.81 (90.05-168.57)	**0.046**	105.67 (80.55-148.60)	107.11 (87.5-153.77)	0.686
PT, median (IQR), s	1.02 (0.97-1.08)	1.03 (0.97-1.07)	0.924	1.03 (0.97-1.08)	1.03 (0.97-1.07)	0.725
INR, median (IQR), %	11.80 (11.20-12.60)	11.80 (11.10-12.80)	0.918	11.90 (11.20-12.65)	12.00 (11.2-13.00)	0.477
TB, median (IQR), μmol/L	14.96 (11.53-20.58)	16.02 (12.50-20.00)	0.666	14.90 (11.75-18.35)	16.74 (12.6-20.37)	0.119
ALT, median (IQR), U/L	26.00 (17.00-42.75)	23.00 (15.00-36.00)	0.136	24.00 (16.00-33.00)	23.00 (19.0-42.00)	0.632
AST, median (IQR), U/L	27.00 (21.25-38.00)	25.00 (20.00-33.00)	**0.042**	27.00 (21.50-34.50)	25.00 (20.0-34.00)	0.438
ALP, median (IQR), U/L	97.50 (78.25-152.00)	94.00 (75.00-114.00)	0.055	89.00 (74.00-117.00)	95.00 (71.0-117.00)	0.696
GGT, median (IQR), U/L	57.50 (27.00-169.50)	42.00 (25.00-74.00)	0.055	42.00 (24.50-107.00)	48.00 (30.0-84.00)	0.479
AFP, median (IQR), ng/mL	2.88 (1.94-4.39)	2.60 (1.88-5.01)	0.906	3.10 (2.01-5.52)	2.90 (1.90-5.01)	0.736
CA199, median (IQR), U/mL	50.77 (16.51-446.95)	28.03 (11.41-92.43)	**0.003**	28.09 (14.65-98.44)	30.36 (12.2-111.70)	0.935
CA125, median (IQR), U/ml	16.58 (9.08-45.84)	14.50 (7.93-19.30)	0.086	14.17 (8.87-30.87)	12.43 (7.25-18.38)	0.322
CEA, median (IQR), ng/mL	2.79 (1.61-5.01)	2.56 (1.38-4.36)	0.500	2.71 (1.63-4.64)	2.85 (1.44-4.42)	0.850
Child–Pugh, n (%)			0.121			0.774
A	216 (91.5)	66 (97.1)		88 (94.6)	45 (95.7)	
B	20 (8.5)	2 (2.9)		5 (5.4)	2 (4.3)	
Nerve invasion, n (%)	62 (26.3)	10 (14.7)	**0.048**	18 (19.4)	9 (19.1)	0.977

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 2. The baseline characteristics of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM (continued)

Variables	Before PSM (n = 304)		p value	After PSM (n =140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Differentiation, n (%)			0.081			0.953
Poor	129 (54.7)	29 (42.6)		46 (49.5)	23 (48.9)	
Moderate / Well	107 (45.3)	39 (57.4)		47 (50.5)	24 (51.1)	
Satellite nodules, n (%)	17 (7.2)	5 (7.4)	0.967	6 (6.5)	4 (8.5)	0.655
Lymphatic metastasis, n (%)	50 (21.2)	5 (7.4)	**0.009**	8 (8.6)	4 (8.5)	0.985
Capsular invasion, n (%)	108 (45.8)	24 (35.3)	0.125	38 (40.9)	18 (38.3)	0.770
TNM, n (%)			**< 0.001**			0.717
I/II	121 (51.3)	52 (76.5)		68 (73.1)	33 (70.2)	
III/IV	115 (48.7)	16 (23.5)		25 (26.9)	14 (29.8)	
Adjuvant therapy, n (%)	80 (33.9)	13 (19.1)	**0.020**	28 (30.1)	9 (19.1)	0.165

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 3. The baseline characteristics of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 322)		p value	After PSM (n = 88)		p value
	OLR (n = 263)	LLR (n = 59)		OLR (n = 57)	LLR (n = 31)	
Age, median (IQR), years	59.00 (51.00-65.00)	59.00 (49.00-68.00)	0.787	61.00 (51.00-64.50)	51.00 (48.00-66.00)	0.296
Gender			0.740			0.947
Female, n (%)	123 (46.8)	29 (49.2)		28 (49.1)	15 (48.4)	
Male, n (%)	140 (53.2)	30 (50.8)		29 (50.9)	16 (51.6)	
Short stature, median (IQR), m	1.63 (1.57-1.69)	1.62 (1.57-1.68)	0.788	1.61 (1.54-1.69)	1.63 (1.57-1.68)	0.501
Weight, median (IQR), Kg	60.00 (53.10-66.01)	65.00 (58.00-71.00)	**0.003**	62.00 (54.75-69.50)	64.00 (57.00-71.00)	0.458
BMI, median (IQR), kg/m^2	22.84 (20.84-24.88)	24.91 (21.91-27.34)	**< 0.001**	24.08 (21.75-26.51)	24.21 (22.07-26.42)	0.797
Hypertension, n (%)	59 (22.4)	13 (22.0)	0.947	10 (17.5)	6 (19.4)	0.833
Diabetes, n (%)	25 (9.5)	8 (13.6)	0.353	6 (10.5)	3 (9.7)	0.900
Alcohol, n (%)	60 (22.8)	17 (28.8)	0.329	15 (26.3)	8 (25.8)	0.959
HBV, n (%)	72 (27.4)	15 (25.4)	0.760	15 (26.3)	10 (32.3)	0.555

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 3. The baseline characteristics of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM (continued)

Variables	Before PSM (*n* = 322)		*p* value	After PSM (*n* = 88)		*p* value
	OLR (*n* = 263)	LLR (*n* = 59)		OLR (*n* = 57)	LLR (*n* = 31)	
HCV, *n* (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
WBC, median (IQR), 10^9/L	6.95 (5.64-8.16)	7.11 (5.65-8.77)	0.724	7.01 (5.80-7.98)	6.14 (4.87-7.71)	0.275
NE, median (IQR), 10^9/L	4.59 (3.65-5.75)	4.52 (3.60-6.03)	0.765	4.51 (3.41-5.54)	4.14 (2.77-5.34)	0.189
Lym, median (IQR), 10^9/L	1.51 (1.17-1.83)	1.61 (1.29-1.89)	0.098	1.59 (1.21-1.88)	1.62 (1.25-1.96)	0.878
NLR, median (IQR), %	3.08 (2.22-4.56)	2.55 (2.10-3.68)	0.066	2.82 (2.16-3.80)	2.41 (1.95-2.90)	0.088
PLT, median (IQR), 10^9/L	190.00 (143.00-241.00)	233.00 (187.00-292.00)	**< 0.001**	197.00 (154.00-245.50)	223.00 (182.00-280.00)	0.063
PLR, median (IQR), %	126.11 (91.93-180.45)	145.60 (102.38-190.27)	0.097	131.36 (93.89-166.49)	145.60 (96.79-171.26)	0.424
PT, median (IQR), s	1.02 (0.97-1.08)	1.00 (0.94-1.07)	0.224	1.01 (0.94-1.04)	0.98 (0.93-1.07)	0.813
INR, median (IQR), %	11.90 (11.20-12.90)	11.90 (11.00-12.70)	0.457	11.70 (11.00-12.75)	12.10 (10.90-13.00)	0.366
TB, median (IQR), μmol/L	13.60 (10.70-19.20)	11.50 (8.84-15.40)	**0.004**	13.40 (10.20-18.25)	10.90 (9.10-16.23)	0.085
ALT, median (IQR), U/L	25.00 (16.00-40.00)	19.00 (13.00-31.00)	**0.005**	23.00 (17.50-33.00)	20.00 (17.00-38.00)	0.717
AST, median (IQR), U/L	31.00 (24.00-43.00)	25.00 (21.00-31.00)	**< 0.001**	30.00 (23.00-35.00)	27.00 (24.00-38.00)	0.993
ALP, median (IQR), U/L	128.00 (99.00-191.00)	99.00 (81.00-122.00)	**< 0.001**	102.00 (84.00-125.50)	98.00 (85.00-120.00)	0.817
GGT, median (IQR), U/L	88.00 (48.00-185.00)	51.00 (33.00-82.00)	**< 0.001**	63.00 (38.50-100.50)	52.00 (34.00-98.00)	0.521
AFP, median (IQR), ng/mL	3.50 (2.24-7.01)	2.70 (1.72-4.74)	**0.018**	3.40 (2.15-5.38)	3.20 (1.76-5.90)	0.872
CA199, median (IQR), U/mL	105.10 (21.47-898.90)	54.86 (16.50-762.68)	0.431	86.87 (19.17-830.44)	55.51 (17.44-664.34)	0.972
CA125, median (IQR), U/ml	27.60 (11.66-94.97)	19.70 (9.58-44.67)	0.146	22.91 (7.91-84.84)	15.00 (6.42-31.73)	0.233
CEA, median (IQR), ng/mL	3.03 (1.59-7.60)	2.83 (1.66-9.39)	0.840	2.73 (1.41-4.41)	2.45 (0.96-10.00)	0.990
Child–Pugh, *n* (%)			0.741			0.920
A	244 (92.8)	54 (91.5)		53 (93.0)	29 (93.5)	
B	19 (7.2)	5 (8.5)		4 (7.0)	2 (6.5)	
Nerve invasion, *n* (%)	29 (11.0)	2 (3.4)	0.072	5 (8.8)	2 (6.5)	0.701
Differentiation, *n* (%)			0.073			0.349
Poor	154 (58.6)	27 (45.8)		28 (49.1)	12 (38.7)	
Moderate / Well	109 (41.4)	32 (54.2)		29 (50.9)	19 (61.3)	
Satellite nodules, *n* (%)	48 (18.3)	5 (8.5)	0.067	6 (10.5)	5 (16.1)	0.448
Lymphatic metastasis, *n* (%)	65 (24.7)	3 (5.1)	**0.001**	8 (14.0)	3 (9.7)	0.555
Capsular invasion, *n* (%)	165 (62.7)	29 (49.2)	0.054	31 (54.4)	18 (58.1)	0.740
TNM, *n* (%)			**< 0.001**			0.519
I/II	107 (40.7)	42 (71.2)		29 (50.9)	18 (58.1)	
III/IV	156 (59.3)	17 (28.8)		28 (49.1)	13 (41.9)	
Adjuvant therapy, *n* (%)	93 (35.4)	14 (23.7)	0.086	22 (38.6)	8 (25.8)	0.227

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 4. The surgical outcomes of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 304)		p value	After PSM (n = 140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Operation time (IQR), min	242.50 (179.50-287.50)	187.50 (153.75-240.00)	**0.038**	215.00 (170.00-281.25)	180.00 (152.-230.00)	0.103
Blood loss (IQR), mL	200.00 (20.00-300.00)	75.00 (20.00-112.50)	**0.001**	125.00 (27.50-200.00)	100.00 (20.0-150.00)	**0.016**
CCI (IQR)	20.90 (8.70-22.60)	8.70 (8.70-22.60)	**0.047**	8.70 (8.70-22.60)	8.70 (8.70-22.60)	**0.017**
CD, n (%)	60 (25.4)	8 (11.7)	**0.017**	23 (24.7)	5 (10.6)	**0.049**
Lymph node dissection, n (%)	89 (37.7)	16 (23.5)	**0.030**	26 (27.9)	10 (21.2)	0.393
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	3.00 (3.00-5.00)	**0.043**	4.00 (3.00-5.00)	3.00 (2.25-4.75)	0.184
Postoperative discharge time (IQR), d	9.00 (7.00-11.00)	6.00 (5.00-8.00)	< 0.001	9.00 (7.00-11.00)	6.00 (5.00-9.00)	< 0.001

Data are presented as n (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; CCI, charlson comorbidity index; CD, Clavien–Dindo ≥ III; IQR, interquartile range.

Table 5. The surgical outcomes of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 322)		p value	After PSM (n = 88)		p value
	OLR (n = 263)	LLR (n = 59)		OLR (n = 57)	LLR (n = 31)	
Operation time (IQR), min	252.50 (181.25-313.75)	270.00 (180.00-345.00)	0.527	235.00 (177.50-337.50)	332.50 (257.50-422.50)	0.062
Blood loss (IQR), mL	300.00 (200.00-500.00)	100.00 (20.00-200.00)	**< 0.001**	325.00 (200.00-500.00)	100.00 (20.00-225.00)	**0.001**
CCI (IQR)	8.70 (8.70-22.60)	8.70 (8.70-19.13)	0.233	22.60 (8.70-25.10)	8.70 (8.70-12.18)	**0.035**
CD, n (%)	39 (14.8)	3 (5.0)	0.053	13 (22.8)	1 (3.2)	**0.016**
Lymph node dissection, n (%)	117 (44.4)	21 (35.5)	0.212	21 (36.8)	12 (38.7)	0.863
Length of hospital stay (IQR), d	14.00 (12.00-17.00)	10.00 (8.75-15.00)	**< 0.001**	12.50 (10.25-18.00)	11.00 (9.00-17.00)	0.127
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	4.00 (2.00-6.00)	0.658	4.00 (3.00-5.00)	5.00 (3.00-6.00)	0.322
Postoperative discharge time (IQR), d	9.00 (8.00-12.00)	6.50 (5.00-8.00)	**< 0.001**	10.00 (7.00-11.75)	7.00 (5.00-10.00)	**0.010**

Data are presented as n (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; CCI, charlson comorbidity index; CD, Clavien–Dindo ≥ III; IQR, interquartile range.

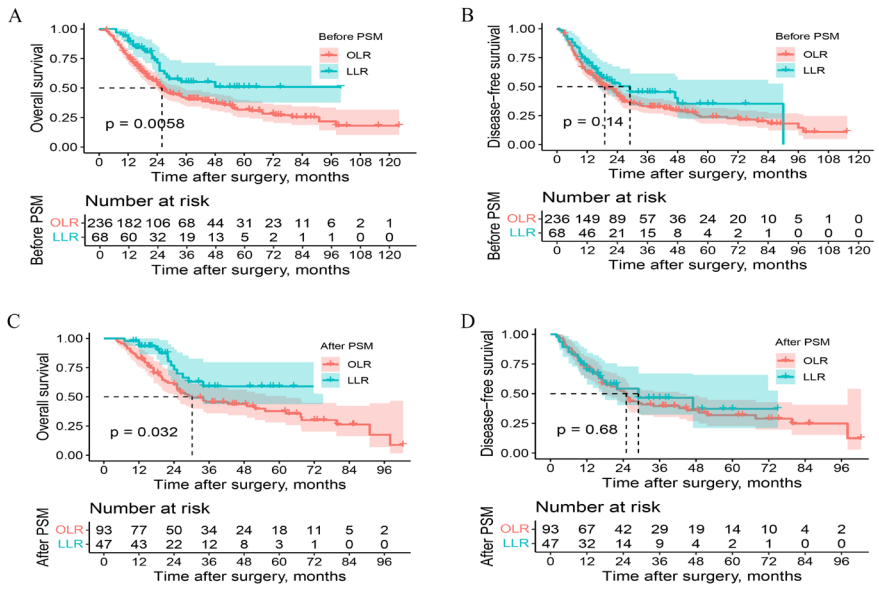

Figure 2. Kaplan–Meier curves estimating OS and DFS of ICC patients in the low TBS group before and after PSM. (A, B) OS and DFS of ICC patients who underwent LLR or OLR before PSM; **(C, D)** OS and RFS of ICC patients who underwent LLR or OLR after PSM. ICC, intrahepatic cholangiocarcinoma; PSM, propensity score matching; LLR, laparoscopic liver resection; OLR, open liver resection; OS, overall survival; DFS, disease-free survival.

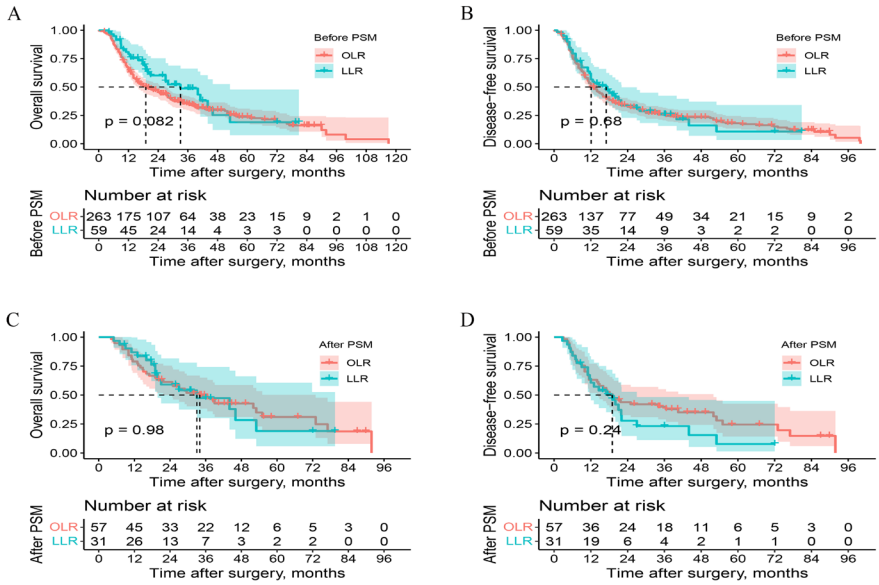

Figure 3. Kaplan–Meier curves estimating OS and DFS of ICC patients in the high TBS group before and after PSM. (A, B) OS and DFS of ICC patients who underwent LLR or OLR before PSM; **(C, D)** OS and RFS of ICC patients who underwent LLR or OLR after PSM. ICC, intrahepatic cholangiocarcinoma; PSM, propensity score matching; LLR, laparoscopic liver resection; OLR, open liver resection; OS, overall survival; DFS, disease-free survival.

5.1 percent; $p = 0.001$) and TNM stage (I/II: 40.7 *vs.* 71.2 percent; III/IV: 59.3 *vs.* 28.8 percent; $p < 0.001$). After PSM, the OLR group consisted of 31 patients, and the LLR group included 57 patients, with the disparities between the groups being effectively mitigated.

3.3. Perioperative outcomes between different surgical procedures in the low- and high-TBS groups

Table 4 provides the surgical outcomes in the low-TBS cohort. Before PSM, the operation time (242.50 *vs.* 187.50 min; $p = 0.038$), blood loss (200.00 *vs.* 75.00 mL; $p = 0.001$), waiting time for surgery (4.00 *vs.* 3.00 d; $p = 0.043$), incidence of CDc grade ≥ IIIa complications (25.4 *vs.* 11.7 percent, $p = 0.017$), CCI (20.9 *vs.* 8.70; $p = 0.047$), and postoperative discharge time (9.00 *vs.* 6.00 d; $p = 0.001$) were greater in the OLR group. After PSM,

LLR was still associated with less blood loss (125.00 *vs.* 100.00 mL; $p = 0.016$), lower CCI (8.7 *vs.* 8.7; $p = 0.017$), a decreased incidence rate of CDc grade ≥ IIIa complications (24.7 *vs.* 10.6 percent; $p = 0.049$) and a shorter postoperative discharge time (9.00 *vs.* 6.00 d; $p < 0.001$).

Table 5 presents the surgical outcomes in the high-TBS cohort. Before PSM, the LLR group presented reduced blood loss (300.00 *vs.* 100.00 mL; $p < 0.001$) and a shorter postoperative discharge time (9.00 *vs.* 6.50 d; $p = 0.010$). After PSM, the LLR group was associated with reduced blood loss (325.00 *vs.* 100.00 mL; $p = 0.001$), lower CCI (22.60 *vs*. 8.70; $p = 0.035$), a decreased incidence of CDc grade ≥ IIIa complications (22.8 *vs.* 3.2 percent; $p = 0.016$) and a shorter postoperative discharge time (10.00 *vs.* 7.00 d; $p = 0.010$).

3.4. Analysis of OS and RFS between different surgical procedures in the low- and high-TBS groups

Figure 2 shows a comparative analysis of the long-term outcomes among patients who underwent LLR and OLR in the low-TBS cohort. Before PSM, the results indicated that LLR exhibited superior OS, with LLR patients demonstrating higher OS rates at 1, 3, and 5 years than OLR patients (1 year: 94.1% *vs.* 77.9%; 3 years: 55.1%

Table 6. Univariable analysis and Multivariate Analysis for OS of ICC patients in the low TBS cohort after PSM

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years	0.997	0.976-1.018	0.753			
Gender, female *vs.* male	1.660	1.033-2.668	**0.036**	1.304	0.674-2.523	0.430
Short stature, m	0.070	0.004-1.158	0.063	0.343	0.008-15.163	0.580
Weight, Kg	0.987	0.967-1.006	0.180			
BMI, kg/m^2	0.988	0.925-1.055	0.709			
Hypertension	0.902	0.520-1.562	0.712			
Diabetes	0.453	0.165-1.244	0.124			
Alcohol	0.701	0.389-1.261	0.236			
HBV	1.015	0.618-1.668	0.953			
HCV	NA	NA	NA			
WBC, 10^9/L	1.029	0.902-1.175	0.670			
NE, 10^9/L	1.063	0.912-1.239	0.437			
Lym, 10^9/L	0.837	0.546-1.283	0.414			
NLR	1.043	0.977-1.114	0.208			
PLT, 10^9/L	1.002	0.999-1.006	0.132			
PLR,	1.004	1.000-1.008	**0.026**	1.002	0.997-1.006	0.499
PT, s	0.947	0.841-1.065	0.363			
INR	0.613	0.182-2.066	0.430			
TB, μmol/L	1.003	0.995-1.012	0.423			
ALT, U/L	1.004	1.000-1.007	0.069	1.002	0.997-1.007	0.362
AST, U/L	1.002	0.999-1.005	0.233			
ALP, U/L	1.004	1.001-1.006	**0.002**	1.003	0.999-1.007	0.199
GGT, U/L	1.002	1.000-1.004	**0.040**	0.999	0.996-1.002	0.638
AFP, ng/mL	0.999	0.996-1.002	0.389			
CA199, U/mL	1.001	1.000-1.002	0.056	1.000	1.000-1.001	0.349
CA125, U/mL	1.003	1.001-1.006	**0.006**	1.004	1.001-1.007	**0.003**
CEA, ng/mL	1.003	0.995-1.010	0.526			
Child–Pugh, A *vs.* B	0.930	0.335-2.581	0.890			
Nerve invasion	1.813	1.019-3.226	**0.043**	1.574	0.838-2.955	0.158
Differentiation, Poor *vs.* Moderate / Well	0.761	0.474-1.222	0.259			
Satellite nodules	1.536	0.661-3.571	0.319			
Lymph node dissection	1.163	0.670-2.020	0.591			
Lymphatic metastasis	3.287	1.602-6.747	**0.001**	3.081	1.394-6.808	**0.005**
Capsular invasion	0.916	0.560-1.496	0.726			
TNM, I/II *vs.* III/IV	0.892	0.514-1.549	0.686			
Surgical approach, LLR *vs.* OLR	0.522	0.284-0.959	**0.036**	0.445	0.235-0.843	**0.013**
Blood loss, ml	1.001	0.999-1.002	0.373			
CCI	1.007	0.974-1.041	0.678			
CD	0.550	0.281-1.077	0.081	1.154	0.532-2.500	0.717
Adjuvant therapy	1.045	0.625-1.747	0.868			

Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; PSM, propensity score matching; ***OS***, overall survival; ***HR***, hazard ratio; ***CI***, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; LLR, laparoscopic liver resection; OLR, open liver resection; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III.

vs. 40.6%; 5 years: 50.9% *vs*. 31.7%, $p = 0.0058$). However, both groups presented similar DFS ($p = 0.14$). After PSM, the LLR group continued to have a better OS than the OLR group ($p = 0.032$), while DFS was comparable between the two groups. Notably, the median DFS time in the LLR group appeared to be longer than that in the OLR group (29 months *vs*. 25 months, $p = 0.068$).

In the high TBS cohort, Figure 3 shows that before PSM, the OS in the LLR group is comparable to that in the OLR group. However, the median survival time was seemingly superior in the LLR group than in the OLR group (33 months versus 19 months, $p = 0.082$), with no statistically significant difference in DFS between the two groups ($p = 0.68$). After PSM, there was no significant difference in OS ($p = 0.98$) or DFS ($p = 0.24$) between the two groups.

3.5. Univariable and multivariable Cox regression analyses of OS in the low- and high-TBS cohorts

Table 5 presents the results of Cox regression analysis exploring risk factors for OS in the low-TBS cohort. Univariate Cox regression analysis revealed that sex, PLR, ALP, γ-glutamyl transpeptidase (GGT), CA125, nerve invasion, lymphatic metastasis and surgical

Table 7. Univariable analysis and Multivariate Analysis for OS of ICC patients in the high TBS cohort after PSM

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years	1.010	0.986-1.034	0.434			
Gender, female *vs.* male	0.701	0.405-1.215	0.206			
Short stature, m	3.520	0.157-78.981	0.428			
Weight, Kg	1.005	0.982-1.029	0.660			
BMI, kg/m^2	1.008	0.925-1.098	0.855			
Hypertension	0.713	0.322-1.583	0.406			
Diabetes	1.288	0.546-3.039	0.563			
Alcohol	2.067	1.154-3.701	**0.015**	2.081	1.046-4.138	**0.037**
HBV	0.849	0.452-1.598	0.612			
HCV	NA	NA	NA			
WBC, 10^9/L	1.084	0.958-1.226	0.199			
NE, 10^9/L	1.143	0.993-1.314	0.062	0.989	0.779-1.257	0.931
Lym, 10^9/L	0.773	0.461-1.298	0.330			
NLR	1.128	0.981-1.297	0.090	1.049	0.820-1.342	0.705
PLT, 10^9/L	1.001	0.999-1.004	0.324			
PLR,	1.002	0.999-1.006	0.120			
PT, s	1.069	0.856-1.334	0.557			
INR	0.188	0.007-5.128	0.322			
TB, μmol/L	1.002	1.000-1.004	0.075	0.993	0.982-1.004	0.196
ALT, U/L	1.001	0.996-1.005	0.708			
AST, U/L	1.000	0.996-1.004	0.861			
ALP, U/L	1.003	1.000-1.005	**0.029**	1.003	0.993-1.013	0.581
GGT, U/L	1.006	1.002-1.010	**0.004**	1.000	0.991-1.009	0.951
AFP, ng/mL	1.000	0.998-1.002	0.706			
CA199, U/mL	1.001	1.000-1.001	**0.015**	1.001	1.000-1.001	0.150
CA125, U/mL	1.003	1.000-1.005	**0.016**	1.002	1.000-1.004	0.070
CEA, ng/mL	1.002	1.000-1.004	**0.027**	1.002	1.000-1.004	**0.044**
Child–Pugh, A *vs.* B	3.935	1.647-9.405	**0.002**	0.091	0.009-0.930	**0.043**
Nerve invasion	3.021	1.179-7.742	**0.021**	1.079	0.339-3.435	0.897
Differentiation, Poor *vs.* Moderate / Well	0.773	0.444-1.349	0.365			
Satellite nodules	1.632	0.793-3.357	0.183			
Lymph node dissection	0.978	0.561-1.706	0.937			
Lymphatic metastasis	1.762	0.824-3.769	0.144			
Capsular invasion	1.008	0.556-1.826	0.980			
TNM, I/II *vs.* III/IV	0.920	0.524-1.618	0.773			
Surgical approach, LLR *vs.* OLR	1.008	0.556-1.826	0.980			
Blood loss, mL	1.001	0.999-1.002	0.478			
CCI	0.988	0.954-1.023	0.508			
CD	0.914	0.445-1.879	0.808			
Adjuvant therapy	0.987	0.556-1.750	0.964			

Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; PSM, propensity score matching; ***OS***, overall survival; ***HR***, hazard ratio; ***CI***, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; LLR, laparoscopic liver resection; OLR, open liver resection; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III.

approach were significantly associated with OS (all $p < 0.05$). Multivariate analysis confirmed that CA125 (HR: 1.004; 95% CI : 1.001–1.007; $p = 0.003$), lymphatic metastasis (HR: 3.081; 95% CI : 1.394–6.808; $p = 0.005$), and surgical approach (HR: 0.445; 95% CI : 0.235–0.843; $p = 0.013$) remained significantly correlated with OS.

Table 6 presents a detailed summary of the Cox regression analyses that were carried out to identify prognostic factors impacting OS in the high-TBS cohort. Univariate Cox regression analysis revealed that alcohol intake, ALP, GGT, CA199, CA125, CEA, Child–Pugh, and nerve invasion were linked to OS (all $p < 0.05$). Multivariate analysis confirmed that alcohol intake (HR: 2.081; 95% CI: 1.046-4.138; $p = 0.037$), CEA (HR: 1.002; 95% CI: 1.000-1.004; $p=0.044$), and Child–Pugh (HR: 0.091; 95% CI: 0.009-0.930; $p = 0.043$), continued to show significant associations with OS (Table 7).

4. Discussion

According to the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), liver resection is indicated for patients with early-stage ICC (*20,21*). In recent years, LLR has been approved as a safe approach and has been applied for the treatment of many liver diseases. However, LLR is not recommended as a routine approach in the treatment of ICC according to the guidelines of AASLD and EASL. Moreover, the application of LLR in radical surgery for ICC lacks sufficient data, leading to uncertainty among clinicians regarding the selection of the optimal surgical procedure (*7*). Tumor size and number are important characteristics of solid tumors and are used in the selection of optimal treatment strategies (*22,23*). TBS, as a metric of tumor size and number, showed better efficacy in evaluating tumor burden and predicting long-term survival than tumor size and number (*11,14*).

In this study, through analyzing the clinical and follow-up data of 626 ICC patients from a multicenter database, several interesting findings were obtained. First, TBS, which is associated with poor tumor-related characteristics, may be a good indicator for predicting the long-term outcomes in ICC. Second, compared to OLR, LLR was associated with faster postoperative recovery. Third, patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term survival for patients with a high TBS grade (> 5.30) compared to those who undergo OLR.

The number and size of tumors represent important morphologic considerations in the staging of ICC (*20,21*). Multiple foci of tumors may represent intrahepatic metastases, and tumor size is considered an important prognostic factor for ICC according to the latest AJCC staging system. Our previous study also revealed that tumor size was an independent risk factor for solitary ICC (*24*). Consequently, TBS may be helpful in capturing the tumor burden and predicting prognosis. For example, Moazzam *et al*. reported that TBS was an important prognostic factor for ICC and was associated with a higher risk of recurrence (*25*). In addition, Li *et al*. demonstrated that TBS could stratify ICC patients into different prognostic groups (*14*). In our study, ICC patients were stratified into two groups based on TBS. Obviously, there were significant differences between the two groups, including TNM stage, PLR and CA199, *etc*. Each of these factors was also an independent prognostic factor for ICC, which may lead to a poorer prognosis for ICC with high TBS grade. In fact, multivariate analysis still revealed that TBS was an independent risk factor for ICC. These findings suggest that TBS is an important prognostic factor for ICC and could be a good indicator for stratifying ICC patients into different groups.

Our results suggest that LLR is associated with faster postoperative recovery. Previous studies have shown that LLR was associated with less blood loss, a lower transfusion rate and a shorter postoperative hospital stay (*26-29*). However, these results focused mainly on the application of LLR in solitary ICC. For large or multiple ICCs, owing to the concerns of difficulty in achieving R0 resection and LND and tumor rupture (*30*), massive bleeding and tumor seeding, few studies have been conducted on this topic. In our study, after PSM, LLR remained related to less blood loss, lower CCI and shorter hospital stay in the high-TBS group. Several researchers have also reported that for large (≥ 5 cm) and multiple (≥ 2) ICCs, LLR could provide no worse short-term outcomes (*9*). These findings suggest that for treating ICC with high TBS grade, although LLR could be a complicated procedure, it remains a feasible and safe choice.

Our results further suggest that patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term survival for patients with a high TBS grade (> 5.30) compared to those who undergo OLR. In the low-TBS group, survival analysis revealed that LLR had better OS than OLR before and after PSM. Indeed, in the Cox regression analysis, the surgical procedure was an independent prognostic factor for ICC. Several reasons could explain this issue: the low incidence rate of postoperative complications, the effective initiation of adjuvant therapies and the biologically favorable context provided by laparoscopy (*31,32*). In the high-TBS group, there were no statistically significant differences in OS or DFS between the LLR and OLR groups. These findings, together with those of other studies (*33*), lead us to conclude that LLR offers ICC patients a comparable and even better long-term prognosis than OLR, and this conclusion is more applicable in patients with low TBS scores.

One of the main concerns for LLR in treating ICC is the difficulty in performing LND. Indeed, the role

of LND for ICC remains controversial (*34,35*). Many previous studies urged surgeons to conduct LND as a routine procedure to provide accurate staging for ICC and improve survival. Consequently, routine LND is recommended by many experts and guidelines. However, some scholars argued against this because patients did not benefit from LND (*36*), which was also proven in our previous study (*37*). In this study, we found that more LND was performed in the high-TBS group, possibly because large or multiple ICCs were more likely to have positive lymph node status based on the preoperative imaging or intraoperative assessment. However, there was no significant difference in the rate of lymph node metastasis between the low- and high-TBS groups. In addition, there was no difference in the LND rate between the LLR and OLR groups in either the low or high TBS group after PSM. These findings are consistent with several studies (*38,39*). Furthermore, Ratti *et al*. revealed that for patients with biliary cancers, LND performed *via* a laparoscopic apparatus was associated with lower lymphadenectomy-related morbidity (*27*). These findings lead us to conclude that LND is no longer a hindrance to the application of LLR in treating ICC.

Multivariate Cox regression analysis was used to explore independent prognostic factors for ICC. Similar to the findings of previous studies, high CA125 and lymph node metastasis were poor prognostic factors in the low-TBS group (*40,41*), and patients with high CEA had significantly worse OS in the high-TBS group (*42*). Our finding that Child-Pugh class B score is a poor prognostic predictor is supported by many other studies (*43-45*). The Child–Pugh grade is used to evaluate the hepatic function reserve before treatment. However, recent studies revealed that a poorer hepatic reserve might lead to a deficiency of immune surveillance and defense by the liver; thus, the elimination of residual and migrating tumor cells by the immune system was impaired, which could cause tumor progression (*43,46,47*). Alcohol consumption was believed to be a risk factor for developing ICC (*48*), and it was identified to be a poor prognostic factor for ICC in the high-TBS group. However, the impact of alcohol consumption on the prognosis of individuals with this condition remains uncertain. Only a recent study revealed that it affected the prognosis of patients with recurrent ICC (*49*). Based on the findings in our study, reducing alcohol consumption was necessary to reduce the incidence and improve the prognosis of ICC.

Several limitations of the study warrant consideration. First, owing to its retrospective nature, selection bias was inherent, despite efforts to mitigate bias through 1:3 propensity score matching. Second, although TBS is an indicator that has high predictive ability, for multiple ICCs, it cannot reflect the influence of different locations on the long-term outcomes. Furthermore, the study cohort comprised solely individuals from China, thus potentially limiting the generalizability of the findings to populations with different living environments and habits. To enhance the broader applicability of the study results, external validation in diverse ethnic groups is recommended.

In conclusion, our study suggests that TBS is an important prognostic factor for ICC and could stratify ICC patients into groups with different survival outcomes. Compared with OLR, LLR is a safe and feasible option for treating ICC and is associated with faster postoperative recovery. Furthermore, patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term outcome for patients with a high TBS grade (> 5.30) compared to those who undergo OLR.

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Original Article

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mFOLFOX-HAIC+lenvatinib+PD-1 inhibitors versus GC/GS/GEMOX chemotherapy as a first line therapy for advanced biliary tract cancer: A single-center retrospective cohort study

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SUMMARY Biliary tract tumors (BTC) account for about 3% of all digestive system tumors, with rising incidence and limited treatment options, particularly for advanced stages, underscoring the need for innovative therapies. This retrospective cohort study evaluated the safety and efficacy of a novel regimen combining hepatic artery infusion chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX-HAIC) alongside lenvatinib and programmed cell death protein-1 (PD-1) inhibitors (mFOLFOX-HAIC+lenvatinib+PD-1i) compared to standard regimens of gemcitabine plus cisplatin, gemcitabine plus S1, or gemcitabine plus oxaliplatin (GC/GS/GEMOX) in advanced BTC patients treated from March 2019 to November 2023. A total of 89 patients were analyzed, with 55 receiving hepatic arterial infusion chemotherapy and 34 receiving the GC/GS/GEMOX regimens. Among these, 23 patients were in the mFOLFOX-HAIC+lenvatinib+PD-1i group, while 24 were in the GC/GS/GEMOX group. The median progression-free survival (mPFS) for the mFOLFOX-HAIC+lenvatinib+PD-1i group was 15 months compared to 6 months for the GC/GS/GEMOX group. Similarly, the median overall survival (mOS) was 20 months for the mFOLFOX-HAIC+lenvatinib+PD-1i group versus 13 months for the GC/GS/GEMOX group. The objective response rate (ORR) and disease control rate (DCR) for the mFOLFOX-HAIC+lenvatinib+PD-1i group were 48.5% and 87.0%, respectively, both significantly higher than those observed in the GC/GS/GEMOX group at three months of treatment. The incidence of adverse events (AEs) was similar between the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group, at 86.5% and 84.2%, respectively, with no statistically significant difference in complication rates. Overall, mFOLFOX-HAIC+lenvatinib+PD-1i appears to be a safe and well-tolerated treatment for advanced BTC, demonstrating superior mPFS and mOS compared to standard regimens.

Keywords advanced biliary tract cancer, hepatic arterial infusion chemotherapy (HAIC), programmed cell death protein-1 (PD-1), systemic chemotherapy

1. Introduction

Biliary tract cancer (BTC) is the second most common hepatic malignant tumor, accounting for approximately 2% of tumor-related deaths worldwide, with its incidence increasing annually (*1,2*). Surgical resection is considered the only potentially curative treatment. However, 70-80% of individuals are diagnosed at an advanced stage, rendering them ineligible for surgery. For the patients presenting with locally unresectable or distant metastatic disease, systemic therapy provides only a limited survival benefit of approximately 1 year, despite its ability to delay disease progression (*3*).

Biliary tract tumors are mainly supplied by hepatic arteries. Hepatic artery infusion chemotherapy (HAIC) is an effective treatment for BTC. It utilizes the hepatic arterial blood supply to deliver high-dose chemotherapy drug directly to the liver and tumor. Therefore, HAIC takes advantage of the liver's first-pass metabolism and provides liver-directed therapy while minimizing systemic exposure (*4*).

The mFOLFOX-HAIC+lenvatinib+PD-1 inhibitor

(mFOLFOX-HAIC+lenvatinib+PD-1i) treatment has shown good efficacy in the treatment of unresectable hepatocellular carcinoma in recent research conducted over the past two years (*5-7*). Additionally, This regimen has also been explored in clinical practice for advanced biliary tract cancers (*8,9*). The objective of this study is to compare the clinical outcomes of mFOLFOX-HAIC+lenvatinib+PD-1i versus systemic chemotherapy as first-line therapy for advanced BTC patients. The findings of this study may provide new insights into the treatment of advanced BTC and guide the development of future therapeutic strategies.

2. Materials and Methods

After the Institutional Review Board (IRB) of Beijing Tsinghua Changgung Hospital reviewed and approved the patient data analysis, medical records of patients with advanced BTC who underwent HAIC or GC/GS/GEMOX (gemcitabine+cisplatin/ gemcitabine+S1/ gemcitabine+oxaliplatin) chemotherapy at our center from March 2019 to November 2023 were reviewed. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and all participants provided informed consent prior to treatment.

2.1. Patient selection

Patient inclusion criteria for this study were as follows: (*i*) age between 18 and 80 years; (*ii*) diagnosis of advanced BTC confirmed by pathological findings, enhanced CT or MR results; (*iii*) advanced BTC, referred to unresectable due to vascular invasion or lymph node metastasis, assessed by our center's multidisciplinary team (MDT); (*iv*) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-2 prior to undergoing GC/GS/GEMOX chemotherapy or mFOLFOX-HAIC; (*v*) Child-Pugh classification of A or B; (*vi*) hematological criteria: WBC $\geq 3.0\times10^9$/L, Hb $\geq$ 70g/L, PLT $\geq 75\times10^9$; (*vii*) liver function criteria: ALT and AST $\leq$ 5 times the upper limit of normal, serum bilirubin $\leq$ 3 times the upper limit of normal; (*viii*) renal function criteria: CCr $\leq$ 1.5 times the upper limit of normal or creatinine clearance rate $\geq$ 50ml/min; (*ix*) coagulation criteria: INR $\leq$ 2; (*x*) availability of complete follow-up data; and (*xi*) voluntary signing of informed consent.

Exclusion criteria for patients were as follows: (*i*) history of other malignant tumors; (*ii*) prior targeted therapy or immunotherapy before receiving GC/GS/GEMOX chemotherapy or mFOLFOX-HAIC; (*iii*) presence of severe cardiovascular disease; (*iv*) malignant hypertension; (*v*) Child-Pugh classification of C; (*vi*) chronic renal failure; (*vii*) presence of arteriovenous fistula in the liver; (*viii*) severe active infection; (*ix*) severe gastrointestinal bleeding within 6 weeks prior to treatment; (*x*) occurrence of severe thrombosis or thrombotic events within 6 months prior to treatment; and (*xi*) missing clinical data or non-compliance with follow-up.

All laboratory data and enhanced CT or MR images were collected within 1 month before initial treatment. The inclusion and exclusion process of this study was depicted in Figure 1, leading to the final inclusion of 89 patients.

2.2. Data collection

Clinical data were sourced from the electronic medical record system of Beijing Tsinghua Changgung

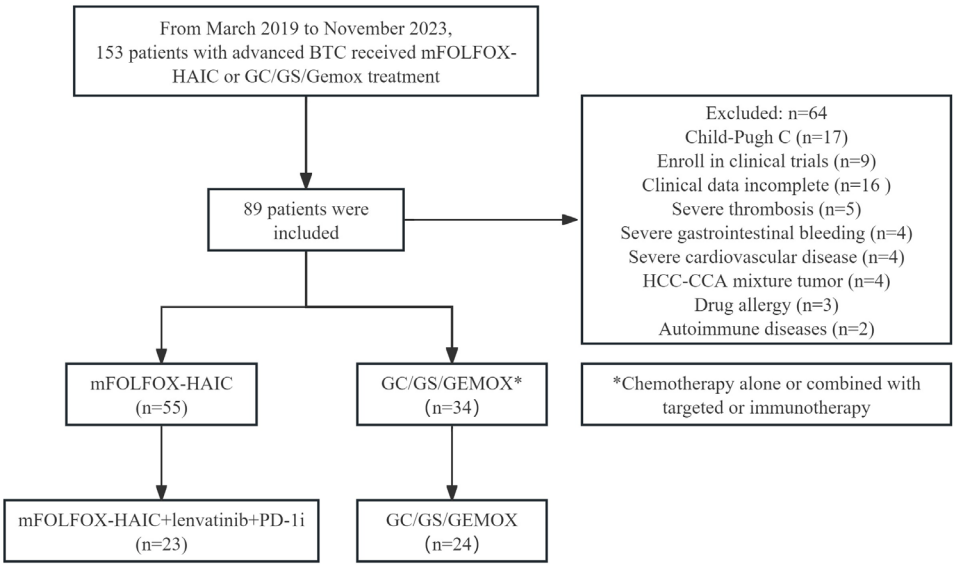

Figure 1. Flow Diagram of Study Design. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; BTC, biliary tract caner; PD-1i, PD-1 inhibitors.

Hospital. The following parameters were collected and analyzed for the study: age, gender, comorbidities, HBV status, ECOG-PS score, white blood cell count (WBC), platelet count (PLT), serum albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), liver function classification (Child-Pugh score), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), protein induced by vitamin K absence II (PIVKA-II), presence of portal vein tumor thrombus, vascular invasion, distant metastases, and underwent percutaneous transhepatic cholangial drainage (PTCD).

2.3. Treatment Protocol

mFOLFOX-HAIC Group: Each HAIC treatment cycle lasted for 3 days. Digital subtraction angiography (DSA) was utilized for accurately select the tumor-feeding artery. To reduce the severity of gastrointestinal adverse reactions, gastric or gastroduodenal artery embolization was performed using spring coils. 5-Fluorouracil was administered continuously for 15 hours per day at a total dose of 1500 mg, while patients received 50 mg of oxaliplatin and 300 mg of calcium folinate every night for two hours. There was a 3 to 4-week or longer interval between two HAIC treatment cycles, and patients underwent 1 to 9 cycles of HAIC treatment. For patients with obstructive jaundice, PTCD drainage was performed, and HAIC was administered once the bilirubin level decreased to three times below the normal range.

GC/GS/GEMOX Group: GC: gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) intravenously on days 1 and 8. GS: Gemcitabine: 1000 mg/m^2 d1, 8 + S1: 80-120 mg/m^2, bid po d1-14. GEMOX: Gemcitabine: 1000 mg/m^2/d1, d8 + Oxaliplatin: 100 mg/m^2/dL. Each chemotherapy cycle was 3-4 weeks or longer due to the patient's intolerance. The patients received 2-10 cycles of chemotherapy. In the case of poor tolerance, some patients treated with GS regimen were changed to albumin paclitaxel combined with the S1 regimen according to the judgment of the attending physician.

PD-1 inhibitors (Tislelizumab, BeiGene Ltd, Beijing, China or Sintilimab, Innovent Biologics Ltd, Suzhou, China) were administered *via* intravenous drip in the duration of systemic chemotherapy or HAIC treatment, with a dose of 200 mg every 3-4 weeks.

Lenvatinib (Japan Eisai Co, Ltd) at a dosage of either 8 mg (≤ 60 kg) or 12 mg (> 60 kg) depending on their body weight. In cases of lenvatinib intolerance, dosage adjustment or discontinuation of the drug was necessary.

Each treatment was discontinued in the event of disease progression (PD), the patient being unable to tolerate toxic or adverse reactions, patient refusal of treatment or change of treatment regimen. Enhanced computed tomography (CT) or magnetic resonance imaging (MR) was performed, while follow-up visits were scheduled every 3 months.

2.4. Outcomes and assessments

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the duration from the commencement of the initial therapy till the occurrence of death owing to any cause or the last follow-up. PFS was referred to the duration from the beginning of the primary therapy till either the progression of the disease or the administration of bridging therapy and transplantation, or the last follow-up. Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was the standard methods employed by radiologists and hepatobiliary surgeons to assess the tumor response. The response criteria involved the determination of complete response (CR), partial response (PR), stable disease (SD), and PD. ORR was defined as the sum of CR and PR, whereas DCR was determined from the sum of CR, PR, and SD. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was utilized to evaluate treatment-related adverse events (AEs).

2.5. Statistical analysis

Baseline characteristics between the two groups were compared using Pearson's chi-square test, Fisher's exact test, or Wilcoxon rank sum test, as appropriate. Mean ± standard error (SE) was used to describe normally distributed variables, while median (interquartile range, IQR) was used for non-normally distributed variables. Kaplan-Meier method was employed for survival analysis, and log-rank test was used to assess differences in survival curves. Covariates with univariate $P < 0.05$ or those considered relevant to patient prognosis were included in multivariate Cox proportional hazards regression model, encompassing patients' basic information, treatment status, tumor status, and other factors to calculate hazard ratios (HR) and confidence intervals (CI). All descriptive and multivariate analyses were carried out using R software version 4.2.2. A two-tailed P-value < 0.05 was deemed statistically significant.

3. Results

3.1. Patient characteristics

From March 2019 to November 2023, a total of 89 patients with advanced BTC participated in this study. Of these, 55 patients received HAIC treatment, while the remaining 34 patients received GC/GS/GEMOX systemic chemotherapy (Chemotherapy alone or combined with targeted or immunotherapy). 23 patients (41.8%) in the HAIC group received lenvatinib+PD-1i (lenvatinib+PD-1 inhibitor) therapy and 24 patients

(70.6%) in the GC/GS/GEMOX (Chemotherapy alone or combined with targeted or immunotherapy) group received GC/GS/GEMOX chemotherapy alone. Patients in the HAIC group received a median of 4 cycles of HAIC, while patients in the GC/GS/GEMOX group received a median of 5 cycles of systemic chemotherapy. Table 1 displayed the demographic data and baseline characteristics of the two groups, which did not show significant differences in other clinical variables.

3.2. Survival

The median follow-up duration was 24 months (range 14.5-36 months), with the last follow-up conducted on July 28, 2024. There was no significant difference in PFS between HAIC group and GC/GS/GEMOX

Table 1. Demographics of patients included in the study

Characteristic	HAIC (*n* = 55)	GC/GS/GEMOX* (*n* = 34)	*p*-value
Patient characteristics			
Age, median (IQR)	65 (53, 68)	62 (55, 71)	0.752
Sex, *n* (%)			0.458
Female	20 (36.4%)	16 (47.1%)	
Male	35 (63.6%)	18 (52.9%)	
Hepatitis, *n* (%)			0.185
Negative	46 (83.6%)	31 (91.3%)	
HBV	9 (16.4%)	3 (8.7%)	
Hypertension, *n* (%)	17 (30.9%)	16 (47.1%)	0.301
Diabetes mellitus, *n* (%)	6 (10.9%)	5 (14.7%)	0.289
Coronary artery disease, *n* (%)	4 (7.3%)	1 (2.9%)	0.684
Child-Pugh grade, *n* (%)			0.785
Grade A	52 (94.5%)	30 (88.2%)	
Grade B	3 (5.5%)	4 (11.8%)	
ECOG-PS, *n* (%)			< 0.001
0	4 (7.3%)	14 (41.2%)	
≥ 1	51 (92.7%)	20 (58.8%)	
HAIC/chemotherapy times, median (IQR)	4 (3, 5)	5 (3, 7)	0.006
PTCD, *n* (%)	26 (47.3%)	14 (41.2%)	0.583
Tumor characteristics			
Size of largest nodule, median (IQR), mm	48 (28, 67)	42 (29, 61)	0.353
Tumor number, *n* (%)			0.049
Single	2 (3.6%)	5 (14.7%)	
Multiple	52 (96.4%)	29 (85.3%)	
Lymph node metastasis, *n* (%)	28 (50.9%)	22 (64.7%)	0.329
Extrahepatic metastasis, *n* (%)	22 (40%)	15 (44.1%)	0.685
Vascular invasion, *n* (%)	45 (81.8%)	22 (64.7%)	0.062
Thrombus, *n* (%)			0.159
Absent	29 (52.7%)	23 (67.6%)	
Portal vein thrombus	26 (47.3%)	11 (32.4%)	
PFS, median (IQR), months	6 (2, 8)	5 (2, 7)	0.123
OS, median (IQR), months	15 (10, 18)	12 (8, 15)	0.243
Laboratory test characteristics			
WBC, median (IQR), $\times10^9$/L	6.25 (4.68, 8.23)	5.98 (4.95, 7.96)	0.421
NEUT, median (IQR), $\times10^9$/L	4.32 (3.08, 5.61)	3.85 (3.23, 4.95)	0.596
LY, median (IQR), $\times10^9$/L	1.31 (0.91, 1.72)	1.26 (1.12, 1.68)	0.651
Hb, mean ± SD, g/L	115.89 ± 19.512	121.85 ± 20.865	0.578
PLT, median (IQR), $\times10^9$/L	201 (134, 252)	216 (168, 263)	0.845
ALB, median (IQR), g/L	38.4 (38.2, 10.8)	40.1 (35.3, 44.8)	0.063
AST, median (IQR), U/L	39.7 (25.8, 55.7)	24.6 (17.3, 43.9)	0.065
ALT, median (IQR), U/L	32 (22.8, 51.5)	25.2 (16.1, 54.2)	0.146
ALP, median (IQR), U/L	168 (118, 361)	109 (89, 205)	0.061
GGT, median (IQR), U/L	129 (71, 261)	121 (53, 221)	0.062
CHE, mean ± SD, U/L	4896 ± 1652	5263 ± 1394	0.087
TBIL, median (IQR), μmol/L	22.5 (12.6, 56.4)	19.8 (12.8, 26.9)	0.048
AFP, median (IQR), ng/mL	4.20 (2.31, 4.31)	4.32 (2.44, 5.85)	0.695
CEA, median (IQR), μg/L	3.28 (1.95, 5.63)	2.87 (2.25, 4.89)	0.924
CA19-9, median (IQR), U/mL	116.8 (19.6, 1052.6)	141.2 (29.6, 1186)	0.296
PIVKA-II, median (IQR), mAU/mL	28.3 (19.5, 68.52)	24.97 (19.9, 51.3)	0.601

HAIC, hepatic artery infusion chemotherapy; IQR, interquartile range; HBV, hepatitis B virus; PTCD, percutaneous transhepatic cholangial drainage; WBC, white blood cell; NEUT, neutrophil; LY, lymphocyte; Hb, hemoglobin; SD, standard deviation; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CHE, cholinesterase; TBIL, total bilirubin; AFP, alpha-Fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PIVKA-II, protein induced by vitamin K absence II. *GC/GS/GEMOX (Chemotherapy alone or combined with targeted or immunotherapy)

group after logistic rank sum test (HR = 0.824; 95% CI 0.501-1.210; P = 0.330) (Figure 2A), as was OS (HR = 0.781; 95% CI 0.465-1.331; P = 0.297) (Figure 2B). As shown in Table 1, the median progression-free survival (mPFS) of HAIC group and GC/GS/GEMOX group were 6 months (95% CI 3.748-8.541) and 5 months (95% CI 2.501-7.412), respectively. The median overall survival (mOS) for the two groups were 15 months and 12 months, respectively. There were no significant differences in mPFS and mOS between the two groups (P = 0.324 and P= 0.875, respectively).

3.3. Impact of lenvatinib and PD-1 inhibitors on the outcomes

23 patients (41.8%) in the HAIC group received lenvatinib and PD-1i (mFOLFOX-HAIC+lenvatinib+PD-1i) and 24 patients (70.6%) in the GC/GS/GEMOX group only received chemotherapy without targeted or immunotherapy (P = 0.001). Table 2 shows the demographic data and baseline characteristics of the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group. There was no significant difference in clinical variables between the two groups except for the ECOG-PS score. ECOG-PS score in the GC/GS/GEMOX group was better than in the mFOLFOX-HAIC+lenvatinib+PD-1i group. The patients in the mFOLFOX-HAIC+lenvatinib+PD-1i group had significantly better PFS (HR = 0.475; 95% CI 0.195 - 0.841; P = 0.004; Figure 3A) and OS (HR = 0.374; 95% CI 0.181 - 0.851; P = 0.002; Figure 3B) than those in the GC/GS/GEMOX group. The mPFS of the mFOLFOX-HAIC+lenvatinib+PD-1i group and GC/GS/GEMOX group were 15 months (95% CI 7.147-24.732) and 6 months (95% CI 2.684-7.875), respectively. The mOS in the mFOLFOX-HAIC+lenvatinib+PD-1i group was 20 months, significantly longer than 13 months observed in the GC/GS/GEMOX group (P < 0.05).

3.4. Tumor response

Treatment response was evaluated in mRECIST criteria at the 3rd-month. The result showed that 3 (13.1%) patients in the mFOLFOX-HAIC+lenvatinib+PD-1i group had PD, 10 (43.5%) patients showed SD, 8 (34.8%) patients achieved PR, and 2 (8.6%) patient achieved CR, resulting in an ORR of 43.5% and DCR of 87.0%. 2 patients who achieved CR underwent surgical resection. The pathology showed necrotic tissue with no tumor cells found. In the GC/GS/GEMOX group, 9 (37.5%) patients had PD, 9 (37.5%) patients had SD, and 6 (25.0%) patients achieved PR; however, no patient achieved CR. The ORR and DCR were 25% and 62.5%, respectively. The mFOLFOX-HAIC+lenvatinib+PD-1i group showed a higher ORR and DCR than the GC/GS/GEMOX group (Table 3).

3.5. Safety and tolerability

As shown in Table 4, based on the CTCAE 5.0 standards, the incidence of AEs for the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group were 91.3% and 87.5%, respectively. In the HAIC group, the most common grade 1-2 AEs were hypertension (78.2%), nausea (78.2%), and fatigue (78.2%) , and the most common grade 3-4 AE was hypertension (47.9%). In the GC/GS/GEMOX group, the most common grade 1-2 AEs were vomiting (75.0%), fatigue (75.0%) and nausea (66.7%), and the most common grade 3-4 AE was leukopenia (13.0%). In terms of grade 1-2 AEs, the incidence of hypertension, hypothyroidism and elevated transaminase levels in

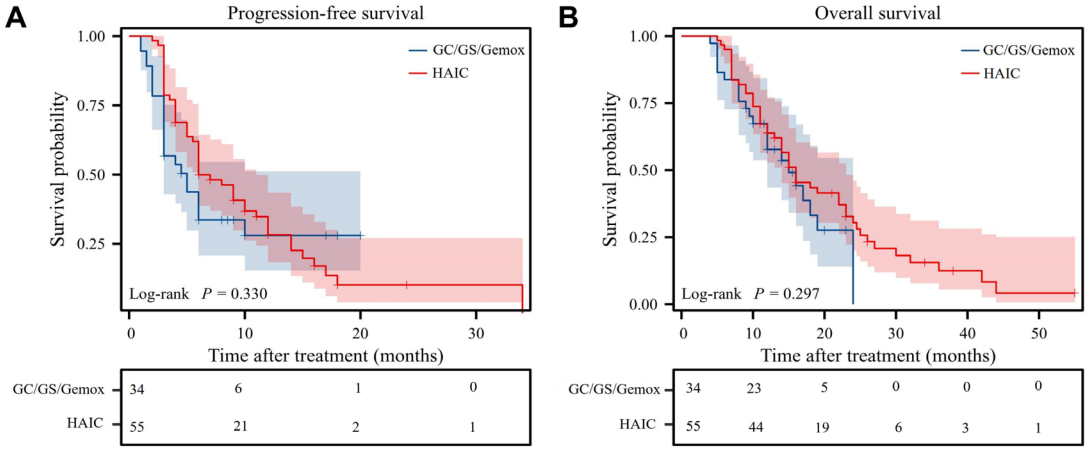

Figure 2. Kaplan-Meier Survival Survival Analysis for HAIC *vs.* GC/GS/GEMOX. Kaplan-Meier analysis of progression-free survival (PFS) and overall survival (OS) in advanced biliary tract cancer patients treated with HAIC versus GC/GS/GEMOX regimens (Chemotherapy alone or combined with targeted or immunotherapy). Panel A details PFS, and Panel B details OS. The curves indicate no significant difference in survival between the two treatment groups, suggesting similar efficacy for both therapeutic strategies. HAIC, hepatic arterial infusion chemotherapy; PFS, progression-free survival; OS, overall survival.

Table 2. Demographic data of the patients who had received PD-1 inhibitors therapy in the study

Characteristic	mFOLFOX-HAIC+lenvatinib+PD-1i (*n* = 23)	GC/GS/GEMOX* (*n* = 24)	*p*-value
Patient characteristics			
Age, median (IQR)	62 (52, 67)	64 (56, 72)	0.585
Sex, *n* (%)			0.386
Female	7 (30.4%)	11 (45.8%)	
Male	16 (69.6%)	13 (54.2%)	
Hepatitis, *n* (%)			0.375
Negative	20 (87.0%)	22 (91.7%)	
HBV	6 (13.0%)	2 (8.3%)	
Hypertension, *n* (%)	11 (47.8%)	12 (50%)	0.789
Diabetes mellitus, *n* (%)	3 (13.0%)	4 (16.7%)	1.023
Coronary artery disease, *n* (%)	3 (13.0%)	2 (8.3%)	0.989
Child-Pugh grade, *n* (%)			1.045
Grade A	21 (91.3%)	21 (87.5%)	
Grade B	2 (8.7%)	3 (12.5%)	
ECOG-PS, *n* (%)			< 0.001
0	1 (4.3%)	11 (45.8%)	
≥ 1	22 (95.7%)	13 (54.2%)	
HAIC/chemotherapy times, median (IQR)	4.12 ± 1.71	4.89 ± 1.28	0.032
PTCD, *n* (%)	11 (47.8%)	11 (45.8%)	0.574
Tumor characteristics			
Size of largest nodule, median (IQR), mm	52.8 ± 28.6	49.2 ± 26.1	0.561
Tumor number, *n* (%)			0.141
Single	2 (8.8%)	2 (8.4%)	
Multiple	21 (91.2%)	22 (91.6%)	
Vascular invasion, *n* (%)	18 (75.3%)	16 (63.4%)	0.125
Lymph node metastasis, *n* (%)	15 (62.8%)	17 (60.7%)	0.814
Extrahepatic metastasis, *n* (%)	9 (34.6%)	11 (46.3%)	0.634
Thrombus, *n* (%)			0.192
Absent	12 (54.8%)	18 (66.7%)	
Portal vein thrombus	11 (43.2%)	6 (33.3%)	
Laboratory test characteristics			
WBC, median (IQR), $\times 10^9$/L	6.12 (4.32, 7.85)	5.89 (4.96, 7.62)	0.561
NEUT, median (IQR) , $\times 10^9$/L	3.96 (3.13, 5.65)	3.71 (3.25, 6.85)	0.451
LY, median (IQR) , $\times 10^9$/L	1.09 (0.91, 1.71)	1.12 (1.09, 1.68)	0.712
Hb, mean ± SD, g/L	118 ± 23.01	119.5 ± 20.13	0.875
PLT, median (IQR) , $\times 10^9$/L	184.8 (142, 239)	210.5 (167, 252)	0.301
ALB, mean ± SD, g/L	39.12 ± 2.58	40.12 ± 4.59	0.125
AST, median (IQR), U/L	39.5 (27.25, 61.78)	32.4 (18.45, 46.78)	0.145
ALT, median (IQR), U/L	34.1 (24, 64.14)	29.8 (15.11, 56.04)	0.198
ALP, median (IQR), U/L	191 (107.4, 359.4)	125.2 (89.3, 241.1)	0.371
GGT, median (IQR), U/L	170 (58.95, 256.85)	105 (37.8, 196.32)	0.091
CHE, median (IQR), U/L	4796.3 (3543.1, 6041.5)	5344.8 (4528.2, 6351.8)	0.148
TBIL, median (IQR), μmol/L	24.84 (13.1, 54.3)	16.03 (10.45, 29.41)	0.157
AFP, median (IQR), ng/mL	3.21 (2.12, 3.95)	3.41 (2.91, 5.442)	0.085
CEA, median (IQR), μg/L	3.65 (2.18, 5.93)	2.41 (2.12, 3.98)	0.506
CA19-9, median (IQR), U/mL	57.10 (9.22, 758.7)	156.47 (43.12, 1181.6)	0.095
PIVKA-II, median (IQR), mAU/mL	35.62 (25.40, 212.52)	24.02 (20.07, 73.48)	0.394

HAIC, hepatic artery infusion chemotherapy; PD-1i, Programmed Death 1 inhibitor; IQR, interquartile range; HBV, hepatitis B virus; PTCD, percutaneous transhepatic cholangial drainage; WBC, white blood cell; NEUT, neutrophil; LY, lymphocyte; Hb, hemoglobin; SD, standard deviation; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CHE, cholinesterase; TBIL, total bilirubin; AFP, alpha-Fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PIVKA-II, protein induced by vitamin K absence II.GC/GS/Gemox*: only chemotherapy.

the mFOLFOX-HAIC+lenvatinib+PD-1i group was significantly higher than that in the GC/GS/GEMOX group ($P < 0.05$). The incidence of hypertension and leukopenia in grade 3-4 AEs was significantly different between the two groups. No grade 5 AEs were observed in either group.

4. Discussion

BTC includes Gall bladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC) and perihilar cholangiocarcinoma (PHCC). They are usually diagnosed in locally advanced or node-positive stage, with a short survival rate (*3,10-14*). BTC is prone to recurrence and metastasis after surgery. The treatment of BTC is a nationwide challenge. This is the first clinical study comparing the efficacy and safety of mFOLFOX-HAIC+lenvatinib+PD-1i with systemic chemotherapy (GC/GS/GEMOX) as first-line therapies for advanced BTC. Our findings indicated that

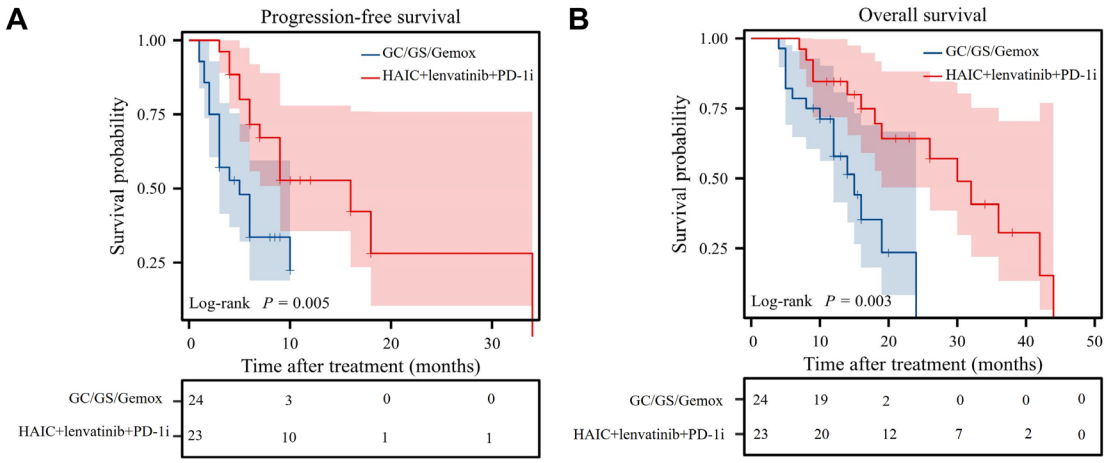

Figure 3. Kaplan-Meier Survival Analysis for mFOLFOX-HAIC+lenvatinib+PD-1i *vs.* GC/GS/GEMOX. The Kaplan-Meier survival curves (Panel A and B) compare progression-free survival and overall survival respectively, between patients receiving mFOLFOX-HAIC+lenvatinib+PD-1i and those treated with the GC/GS/GEMOX regimen. The curves suggest improved life expectancy for the HAIC +lenvatinib+PD-1i group. HAIC, hepatic arterial infusion chemotherapy; PD-1i, PD-1 inhibitors; HR, harzard ratio.

Table 3. Tumor response rates between the two groups at the third month of the treatment

	mFOLFOX-HAIC+lenvatinib+PD1i (n = 23)	GC/GS/GEMOX* (n = 24)	p-value
Tumor response, n (%)			
CR	2 (8.6%)	0 (0%)	0.745
PR	8 (34.8%)	6 (25.0%)	0.785
SD	10 (43.5%)	9 (37.5%)	0.712
PD	3 (13.1%)	9 (37.5%)	0.412
ORR	10 (43.5%)	6 (25.0%)	0.528
DCR	20 (87.0%)	15 (62.5%)	0.378
PFS, median (IQR), months	15 (4, 20)	6 (3, 9)	0.002
OS, median (IQR), months	20 (10, 23)	13 (9, 16)	0.029

HAIC, hepatic artery infusion chemotherapy; 95% CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. GC/GS/GEMOX*: only chemotherapy.

Table 4. The adverse events in the two groups according to Common Terminology Criteria for Adverse Events version 5.0

	Grade 1-2 AEs			Grade 3-4 AEs		
n (%)	mFOLFOX-HAIC+ lenvatinb+PD-1i (n = 23)	GC/GS/ GEMOX (n = 24)	p value	mFOLFOX-HAIC+ lenvatinb+PD-1i (n = 23)	GC/GS/ GEMOX (n = 24)	p value
Nausea	18 (78.2%)	16 (66.7%)	0.064	0 (0)	2 (8.3%)	-
Vomiting	15 (65.2%)	18 (75.0%)	0.162	0 (0)	0 (0)	-
Abdominal pain	13 (56.5%)	9 (39.1%)	0.075	0 (0)	1 (4.2%)	0.140
Abdominal distention	6 (26.1%)	5 (21.7%)	0.408	0 (0)	0 (0)	-
Diarrhea	12 (52.1%)	6 (16.2%)	0.668	1 (4.3%)	1 (4.2%)	0.631
Fever	10 (43.5%)	13 (46.4%)	0.521	2 (8.7%)	0 (0)	0.288
Hypertension	18 (78.2%)	6 (26.1%)	0.021*	11 (47.9%)	1 (4.2%)	0.015*
Hand-foot syndrome	7 (30.4%)	9 (39.1%)	0.449	2 (8.7%)	1 (4.2%)	0.116
Gastric mucosal bleeding	2 (8.7%)	5 (21.7%)	0.223	1 (4.3%)	1 (4.2%)	0.915
Joint pain	1 (4.3%)	5 (21.7%)	0.059	0 (0)	0 (0)	-
Fatigue	18 (78.2%)	18 (75.0%)	0.114	1 (4.3%)	1 (4.2%)	0.915
Infection	4 (17.4%)	3 (13.0%)	0.640	1 (4.3%)	1 (4.2%)	0.631
Thrombocytopenia	14 (60.9%)	11 (47.8%)	0.193	1 (4.3%)	2 (8.7%)	0.915
Leukopenia	8 (34.8%)	9 (39.1%)	0.645	1 (4.3%)	3 (13.0%)	0.035*
Elevated transaminases	15 (65.2%)	7 (30.4%)	0.001*	1 (4.3%)	1 (4.2)	0.525
Elevated bilirubin	6 (26.1%)	3 (13.0%)	0.217	1 (4.3%)	0 (0)	0.288
Immune-mediated pneumonia	0 (0)	0 (0)	-	1 (4.3%)	0 (0)	0.525
Hypothyroidism	3 (13.0%)	0 (0)	0.015*	1 (4.3%)	0 (0)	0.525
Immune-mediated myocarditis	0 (0)	0 (0)	-	1 (4.3%)	0 (0)	0.525

AEs, adverse events; HAIC, hepatic artery infusion chemotherapy; GC/GS/Gemox: only chemotherapy. *Denotes a p-value < 0.05.

mFOLFOX-HAIC+lenvatinib+PD-1i improved survival rates in advanced BTC patients compared to systemic chemotherapy. Especially two patients who underwent mFOLFOX-HAIC+lenvatinib+PD-1i achieved CR and successfully underwent surgical treatment. Although mFOLFOX-HAIC+lenvatinib+PD-1i resulted in a higher incidence of grade 1-2 AEs, such as hypertension and elevated transaminase levels compared to systemic chemotherapy. HAIC did not lead to a higher incidence of grade 3-4 AEs or grade 5 AEs. All AEs could be resolved by effective interventions. These findings represent a potential paradigm shift in advanced BTC treatment. mFOLFOX-HAIC+lenvatinib+PD-1i has the potential to be a safe and effective alternative for first-line treatment for advanced biliary tract cancer.

While doublet chemotherapy with gemcitabine and cisplatin has been regarded as the most effective first-line treatment for the past decade (*3*), its efficacy is often hindered by systemic toxicity, limited drug delivery to the tumor site, and the development of drug resistance. The efficacy of systemic chemotherapy alone remains limited, and there is an urgent need for alternative treatment approaches. Gonzalez-Carmona *et al*. (*15*) demonstrated that the combination of local radiation therapy combined with gemcitabine and cisplatin chemotherapy significantly prolonged survival compared to chemotherapy alone in patients with advanced BTC. Furthermore, this combination therapy was well-tolerated, indicating good tolerability. Edeline *et al*. (*16*) combined selective internal radiotherapy (SIRT) with chemotherapy (gemcitabine and cisplatin) as first-line treatment for unresectable BTC. This regime achieved downstaging and transfer to surgery in 22% of patients.

BTC is often mainly supplied by the hepatic artery. HAIC utilizes the hepatic arterial blood supply to deliver high-dose chemotherapeutics directly to the liver including the tumor. Therefore, HAIC takes advantage of the liver's first-pass metabolism and provides liver-directed therapy while minimizing systemic exposure (*4*). HAIC have the potential to achieve comparable or even superior survival outcomes compared to systemic chemotherapy alone. Konstantinidis *et al*. (*12*) compared the outcomes of patients with unresectable BTC who received HAIC in addition to systemic chemotherapy with those who received systemic chemotherapy alone. The combination of systemic chemotherapy and HAIC improved the survival compared to systemic chemotherapy alone (30.8 vs 18.4 months). Cercek *et al*. (*11*) treated unresectable BTC patients with the HAIC in combination with systemic gemcitabine and oxaliplatin. The authors reported a mPFS of 11.8 months, a 6-month PFS rate of 84.1%, a mOS of 25.0 months, and a 1-year OS rate of 89.5%. In a study conducted by Ishii *et al*. (*17*), patients underwent HAIC with gemcitabine, cisplatin, and 5-fluorouracil were compared to those who underwent systemic gemcitabine and cisplatin treatment. The OS of the HAIC group was superior to that of the standard chemotherapy cohort, as it demonstrated a favorable response and disease control in patients who had previously shown intolerance to the gemcitabine plus cisplatin combination therapy. Wang *et al*. (*18*) conducted a prospective phase II study, showing that HAIC with oxaliplatin and 5-fluorouracil is a promising treatment option for advanced BTC. The study demonstrated notable efficacy in terms of tumor control, with an ORR of 67.6% and a DCR of 89.2%, and exhibited a survival benefit with median PFS, local PFS, and OS of 12.2, 25.0, and 20.5 months, respectively. HAIC could potentially serve as an effective therapeutic alternative for individuals with advanced BTC.

PD-1 inhibitors have emerged as a promising treatment modality in various malignancies by enhancing the immune response against cancer cells through the blockade of the PD-1/PD-L1 interaction. PD-L1 is expressed in approximately half of the BTC patients, which is associated with poor prognosis (*19*). A multicenter phase II study involving 54 patients evaluated the efficacy and safety of nivolumab for advanced BTC patients who had undergone prior treatment (*20*). The study reported an ORR of 22% and a DCR of 59%. Furthermore, the mPFS and mOS were 3.68 months and 14.24 months, respectively. Notably, all patients who responded to treatment exhibited positive PD-L1 expression in their tumors, which was associated with longer PFS. Similarly, a retrospective multicenter study assessed the clinical efficacy and safety of pembrolizumab in GC chemotherapy-refractory BTC patients (*21*). In this study, 51 advanced BTC patients with PD-L1-positive tumors after progressing on first-line GC treatment received pembrolizumab. The ORR was 9.8%, with a mPFS of 2.1 months and a mOS of 6.9 months. Grade 3/4 AEs occurred in only 4 patients (7.8%). Another phase I study evaluated the safety and tolerability of durvalumab (anti-PD-L1 antibody) and tremelimumab (anti-CTLA-4 antibody) in advanced BTC patients who experienced chemotherapy failure (*22*). The mPFS and mOS were 8.1 months and 10.1 months, respectively. This study demonstrated that durvalumab plus tremelimumab combination therapy were well-tolerated and showed promising clinical efficacy. The ORR and DCR of advanced BTC patients treated with PD-1 inhibitors reported by Ye *et al*. (*23*) were 16.7% and 79.6%, respectively, and the mPFS and mOS were 6.6 months and 13.9 months. Deng *et al*. (*24*) reported that treated with PD-1 inhibitors, the mOS, mPFS, and median time to progression (mTTP) of patients with advanced BTC were 19.3 months, 11.6 months, and 11.6 months, respectively, with an ORR of 23.8% and a DCR of 85.7%.

Although immune checkpoint inhibitors (ICIs) alone exhibit limited efficacy, their combination with chemotherapy or radiotherapy has demonstrated

favorable responses in BTC (*25*). The groundbreaking Topaz-1 trial marked the inaugural global phase III study investigating the use of first-line durvalumab in combination with GC chemotheray for advanced BTC treatment (*26*). The results demonstrated a significant improvement in both OS and PFS in the durvalumab plus GC group compared to the placebo plus GC group. Lei *et al*. (*27*) conducted a study comparing the survival outcomes of patients from 22 centers in China and found that the combination of chemotherapy and PD-1 inhibitors provided greater survival benefits than chemotherapy alone. The mPFS was 6.3 months in the combination therapy group compared to 3.8 months in the chemotherapy alone group, and the mOS was 10.7 months in the combination therapy group compared to 9.3 months in the chemotherapy alone group. Gou *et al*. (*28*) conducted a comparative study in advanced BTC patients receiving combination therapy of chemotherapy and PD-1 inhibitors versus chemotherapy alone. The study findings revealed that the addition of PD-1 inhibitors did not significantly improve the ORR and DCR, but it significantly prolonged the PFS.

Researches have shown that targeted therapy, immunotherapy, and conventional chemotherapy in BTC have certain mechanistic links, and the combination of those can improve the prognosis of advanced BTC patients (*19*). Huang *et al*. (*29*) conducted a comparison analysis of first-line treatments for patients with advanced BTC, specifically PD-1/PD-L1 inhibitors plus lenvatinib or gemcitabine/cisplatin (GC). The study reported that patients in the PD-1/PD-L1 inhibitors plus lenvatinib group were more likely to have an Eastern Cooperative Oncology Group (ECOG) performance status value above 1or have ascites. The response rate (RR) was 16.0% in the PD-1/PD-L1 inhibitors plus lenvatinib group compared to 23.1% in the GC group (P = 0.777). The DCR was 52.0% in the PD-1/PD-L1i+lenvatinib group compared to 46.2% in the GC group (P = 0.676). The combination therapy of PD-1/PD-L1 inhibitors plus lenvatinib was associated with a longer PFS compared to the GC group; however, this difference did not reach statistical significance (lenvatinib: 9.5 months, GC: 5.1 months, P = 0.454). Therefore, both PD-1/PD-L1 inhibitors in combination with lenvatinib or GC demonstrated significant efficacy and safety as first-line treatment options for patients with advanced intrahepatic BTC. For patients who refuse or are intolerant to chemotherapy, PD-1/PD-L1 inhibitors plus lenvatinib would be a recommended choice. Xie *et al*. (*30*) administered lenvatinib plus PD-1 inhibitor to patients with chemotherapy-refractory advanced BTC. The mPFS was 5.83 ± 0.76 months. The 3-month and 6-month PFS rates were 80.0% and 32.5%, respectively. The mOS was 14.30 ± 1.30 months. The 12-month and 18-month survival rates were 61.4% and 34.7%, respectively. The ORR was 17.5%, and the DCR was 75.0%. According to a multicenter retrospective real-world study, the combination of PD-1 inhibitors, lenvatinib, and Gemox chemotherapy demonstrated efficacy and tolerability as a treatment regimen for advanced BTC (*31*). Shi *et al*. (*32*) demonstrated that toripalimab in combination with lenvatinib and Gemox showed promise as a first-line regimen for treating advanced BTC, with a mOS of 22.5 months, mPFS of 10.2 months, median duration of response (mDoR) of 11.0 months, and a DCR of 93.3%. Wang *et al*. (*33*) reported that the adding radiotherapy (RT) to toripalimab and lenvatinib may enhance the efficacy for advanced BTC patients. The combination of toripalimab and lenvatinib with RT demonstrated a favorable safety profile, with no significant increase in specific toxicities. Zhu *et al*. (*34*) conducted a retrospective study of patients with advanced BTC who received lenvatinib combined with PD-1/PD-L1 inhibitors plus gemcitabine and oxaliplatin (Gemox) chemotherapy. The study showed a mOS of 13.4 months and a mPFS of 9.27 months. The ORR, DCR, and clinical benefit rate were reported as 43.9%, 91.2%, and 73.7%, respectively. Zhang *et al*. (*35*) discovered that advanced BTC patients who experienced immune-related adverse events (irAEs) following PD-1 inhibitor combination therapy had a higher DCR compared to patients who did not experience irAEs (90.6% *vs.* 70.4%). Additionally, these patients exhibited superior mOS and mPFS compared to those who did not experience irAEs (mOS: 21.2 months *vs.* 10.0 months; mPFS: 9.0 months *vs.* 4.4 months). Notably, Wei *et al*. have provided preliminary evidence demonstrating the safety, tolerability, and potential survival benefits of combined treatment with HAIC, lenvatinib, and PD-1 inhibitors in advanced BTC patients (*8*).

This study had certain limitations. First, its retrospective design limited the analysis to preexisting data, which made the analysis susceptible to potential biases and variations in data collection. Second, the relatively small sample size might have increased the likelihood of findings, and thus, the results should be interpreted with caution.

In conclusion, our study suggested that HAIC in combination with lenvatinib and PD-1 inhibitors has the potential to serve as a safe and effective alternative for first-line treatment of advanced BTC. These findings determined the importance of further research and prospective studies to validate these results and optimize treatment strategies for advanced BTC patients.

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BioScience Trends

Guide for Authors

1. Scope of Articles

BioScience Trends (Print ISSN 1881-7815, Online ISSN 1881-7823) is an international peer-reviewed journal. *BioScience Trends* devotes to publishing the latest and most exciting advances in scientific research. Articles cover fields of life science such as biochemistry, molecular biology, clinical research, public health, medical care system, and social science in order to encourage cooperation and exchange among scientists and clinical researchers.

2. Submission Types

Original Articles should be well-documented, novel, and significant to the field as a whole. An Original Article should be arranged into the following sections: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, and References. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 4 figures and/or tables and 30 references. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined.

Reviews should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of 10 figures and/or tables and 100 references. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 50 references.

Policy Forum articles discuss research and policy issues in areas related to life science such as public health, the medical care system, and social science and may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references.

Communications are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Comments" or "Correspondence". Communications should not exceed 1,500 words in length (excluding references) and should be limited to a maximum of 2 figures and/or tables and 20 references.

Editorials are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references) and should be limited to a maximum of 10 references. Editorials may contain one figure or table.

News articles should report the latest events in health sciences and medical research from around the world. News should not exceed 500 words in length.

Letters should present considered opinions in response to articles published in *BioScience Trends* in the last 6 months or issues of general interest. Letters should not exceed 800 words in length and may contain a maximum of 10 references. Letters may contain one figure or table.

3. Editorial Policies

For publishing and ethical standards, *BioScience Trends* follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals issued by the International Committee of Medical Journal Editors (ICMJE, *https://icmje.org/recommendations*), and the Principles of Transparency and Best Practice in Scholarly Publishing jointly issued by the Committee on Publication Ethics (COPE, *https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing*), the Directory of Open Access Journals (DOAJ, *https://doaj.org/apply/transparency*), the Open Access Scholarly Publishers Association (OASPA, *https://oaspa.org/principles-of-transparency-and-best-practice-in-scholarly-publishing-4*), and the World Association of Medical Editors (WAME, *https://wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing*).

BioScience Trends will perform an especially prompt review to encourage innovative work. All original research will be subjected to a rigorous standard of peer review and will be edited by experienced copy editors to the highest standards.

Ethical Approval of Studies and Informed Consent: For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. When your manuscript contains any case details, personal information and/or images of patients or other individuals, authors must obtain appropriate written consent, permission and release in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. The consent form needs to comply with the relevant legal requirements of your particular jurisdiction, and please do not send signed consent form to *BioScience Trends* to respect your patient's and any other individual's privacy. Please instead describe the information clearly in the Methods (patient consent) section of your manuscript while retaining copies of the signed forms in the event they should be needed. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Reporting Clinical Trials: The ICMJE (*https:// icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html*) defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Registration of clinical trials in a public trial registry at or before the time of first patient enrollment is a condition of consideration for publication in *BioScience Trends*, and the trial registration number will be published at the end of the Abstract. The registry must be independent of for-profit interest and publicly accessible. Reports of trials must conform to CONSORT 2010 guidelines (*https://consort-statement.org/consort-2010*). Articles reporting the results of randomized trials must include the CONSORT flow diagram showing the progress of patients throughout the trial.

Conflict of Interest: All authors are required to disclose any actual or potential conflict of interest including financial interests or relationships with other people or organizations that might raise questions of bias

in the work reported. If no conflict of interest exists for each author, please state "There is no conflict of interest to disclose".

Submission Declaration: When a manuscript is considered for submission to *BioScience Trends*, the authors should confirm that 1) no part of this manuscript is currently under consideration for publication elsewhere; 2) this manuscript does not contain the same information in whole or in part as manuscripts that have been published, accepted, or are under review elsewhere, except in the form of an abstract, a letter to the editor, or part of a published lecture or academic thesis; 3) authorization for publication has been obtained from the authors' employer or institution; and 4) all contributing authors have agreed to submit this manuscript.

Initial Editorial Check: Immediately after submission, the journal's managing editor will perform an initial check of the manuscript. A suitable academic editor will be notified of the submission and invited to check the manuscript and recommend reviewers. Academic editors will check for plagiarism and duplicate publication at this stage. The journal has a formal recusal process in place to help manage potential conflicts of interest of editors. In the event that an editor has a conflict of interest with a submitted manuscript or with the authors, the manuscript, review, and editorial decisions are managed by another designated editor without a conflict of interest related to the manuscript.

Peer Review: *BioScience Trends* operates a single-anonymized review process, which means that reviewers know the names of the authors, but the authors do not know who reviewed their manuscript. All articles are evaluated objectively based on academic content. External peer review of research articles is performed by at least two reviewers, and sometimes the opinions of more reviewers are sought. Peer reviewers are selected based on their expertise and ability to provide quality, constructive, and fair reviews. For research manuscripts, the editors may, in addition, seek the opinion of a statistical reviewer. Every reviewer is expected to evaluate the manuscript in a timely, transparent, and ethical manner, following the COPE guidelines (*https://publicationethics.org/files/cope-ethical-guidelines-peer-reviewers-v2_0.pdf*). We ask authors for sufficient revisions (with a second round of peer review, when necessary) before a final decision is made. Consideration for publication is based on the article's originality, novelty, and scientific soundness, and the appropriateness of its analysis.

Suggested Reviewers: A list of up to 3 reviewers who are qualified to assess the scientific merit of the study is welcomed. Reviewer information including names, affiliations, addresses, and e-mail should be provided at the same time the manuscript is submitted online. Please do not suggest reviewers with known conflicts of interest, including participants or anyone with a stake in the proposed research; anyone from the same institution; former students, advisors, or research collaborators (within the last three years); or close personal contacts. Please note that the Editor-in-Chief may accept one or more of the proposed reviewers or may request a review by other qualified persons.

Language Editing: Manuscripts prepared by authors whose native language is not English should have their work proofread by a native English speaker before submission. If not, this might delay the publication of your manuscript in *BioScience Trends*.

The Editing Support Organization can provide English proofreading, Japanese-English translation, and Chinese-English translation services to authors who want to publish in *BioScience Trends* and need assistance before submitting a manuscript. Authors can visit this organization directly at *https://www.iacmhr.com/iac-eso/support.php?lang=en*. IAC-ESO was established to facilitate manuscript preparation by researchers whose native language is not English and to help edit works intended for international academic journals.

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4. Cover Letter

The manuscript must be accompanied by a cover letter prepared by the corresponding author on behalf of all authors. The letter should indicate the basic findings of the work and their significance. The letter should also include a statement affirming that all authors concur with the submission and that the material submitted for publication has not been published previously or is not under consideration for publication elsewhere. The cover letter should be submitted in PDF format. For an example of Cover Letter, please visit: *https://www.biosciencetrends.com/downcentre* (Download Centre).

5. Submission Checklist

The Submission Checklist should be submitted when submitting a manuscript through the Online Submission System. Please visit Download Centre (*https://www.biosciencetrends.com/downcentre*) and download the Submission Checklist file. We recommend that authors use this checklist when preparing your manuscript to check that all the necessary information is included in your article (if applicable), especially with regard to Ethics Statements.

6. Manuscript Preparation

Manuscripts are suggested to be prepared in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals", as presented at *https://www.ICMJE.org*.

Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (*e.g.* DNA). Single words should not be abbreviated.

Title page: The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; 5) author contribution statements to specify the individual contributions of all authors to this manuscript, and 6) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state "There is no conflict of interest to disclose").

Abstract: The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, News, or Letters, a brief summary of main content in 150 words or fewer should be included in the manuscript. For articles reporting clinical trials, the trial registration number should be stated at the end of the Abstract. Abbreviations must be kept to a minimum and non-standard

abbreviations explained in brackets at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included in the Abstract page.

Introduction: The introduction should provide sufficient background information to make the article intelligible to readers in other disciplines and sufficient context clarifying the significance of the experimental findings

Materials/Patients and Methods: The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance Materials/ Patients and Methods.

Results: The description of the experimental results should be succinct but in sufficient detail to allow the experiments to be analyzed and interpreted by an independent reader. If necessary, subheadings may be used for an orderly presentation. All Figures and Tables should be referred to in the text in order, including those in the Supplementary Data.

Discussion: The data should be interpreted concisely without repeating material already presented in the Results section. Speculation is permissible, but it must be well-founded, and discussion of the wider implications of the findings is encouraged. Conclusions derived from the study should be included in this section.

Acknowledgments: All funding sources (including grant identification) should be credited in the Acknowledgments section. Authors should also describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. If the funding source had no such involvement, the authors should so state.

In addition, people who contributed to the work but who do not meet the criteria for authors should be listed along with their contributions.

References: References should be numbered in the order in which they appear in the text. Citing of unpublished results, personal communications, conference abstracts, and theses in the reference list is not recommended but these sources may be mentioned in the text. In the reference list, cite the names of all authors when there are fifteen or fewer authors; if there are sixteen or more authors, list the first three followed by *et al*. Names of journals should be abbreviated in the style used in PubMed. Authors are responsible for the accuracy of the references. The EndNote Style of *BioScience Trends* could be downloaded at **EndNote** (*https://ircabssagroup.com/examples/ BioScience_Trends.ens*).

Examples are given below:

Example 1 (Sample journal reference):

Inagaki Y, Tang W, Zhang L, Du GH, Xu WF, Kokudo N. Novel aminopeptidase N (APN/CD13) inhibitor 24F can suppress invasion of hepatocellular carcinoma cells as well as angiogenesis. Biosci Trends. 2010; 4:56-60.

Example 2 (Sample journal reference with more than 15 authors):

Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: Collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

Example 3 (Sample book reference):

Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

Example 4 (Sample web page reference):

World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_ en.pdf* (accessed September 23, 2022).

Tables: All tables should be prepared in Microsoft Word or Excel and should be arranged at the end of the manuscript after the References section. Please note that tables should not in image format. All tables should have a concise title and should be numbered consecutively with Arabic numerals. If necessary, additional information should be given below the table.

Figure Legend: The figure legend should be typed on a separate page of the main manuscript and should include a short title and explanation. The legend should be concise but comprehensive and should be understood without referring to the text. Symbols used in figures must be explained. Any individually labeled figure parts or panels (A, B, *etc*.) should be specifically described by part name within the legend.

Figure Preparation: All figures should be clear and cited in numerical order in the text. Figures must fit a one- or two-column format on the journal page: 8.3 cm (3.3 in.) wide for a single column, 17.3 cm (6.8 in.) wide for a double column; maximum height: 24.0 cm (9.5 in.). Please make sure that the symbols and numbers appeared in the figures should be clear. Please make sure that artwork files are in an acceptable format (TIFF or JPEG) at minimum resolution (600 dpi for illustrations, graphs, and annotated artwork, and 300 dpi for micrographs and photographs). Please provide all figures as separate files. Please note that low-resolution images are one of the leading causes of article resubmission and schedule delays.

Units and Symbols: Units and symbols conforming to the International System of Units (SI) should be used for physicochemical quantities. Solidus notation (*e.g.* mg/kg, mg/mL, mol/mm^2/min) should be used. Please refer to the SI Guide *www.bipm.org/en/si/* for standard units.

Supplemental data: Supplemental data might be useful for supporting and enhancing your scientific research and *BioScience Trends* accepts the submission of these materials which will be only published online alongside the electronic version of your article. Supplemental files (figures, tables, and other text materials) should be prepared according to the above guidelines, numbered in Arabic numerals (*e.g.*, Figure S1, Figure S2, and Table S1, Table S2) and referred to in the text. All figures and tables should have titles and legends. All figure legends, tables and supplemental text materials should be placed at the end of the paper. Please note all of these supplemental data should be provided at the time of initial submission and note that the editors reserve the right to limit the size and length of Supplemental Data.

5. Submission Checklist

The Submission Checklist will be useful during the final checking of a manuscript prior to sending it to *BioScience Trends* for review. Please visit Download Centre and download the Submission Checklist file.

6. Online Submission

Manuscripts should be submitted to *BioScience Trends* online at *https://www.biosciencetrends.com/login*. Receipt of your manuscripts submitted online will be acknowledged by an e-mail from Editorial Office containing a reference number, which should be used in all future communications. If for any reason you are unable to submit a file online, please contact the Editorial Office by e-mail at *office@ biosciencetrends.com*

8. Accepted Manuscripts

Page Charge: Page charges will be levied on all manuscripts accepted for publication in *BioScience Trends* (Original Articles / Brief Reports / Reviews / Policy Forum / Communications: $140 per page for black white pages, $340 per page for color pages; News / Letters: a total cost of $600). Under exceptional circumstances, the author(s) may apply to the editorial office for a waiver of the publication charges by stating the reason in the Cover Letter when the manuscript online.

Misconduct: *BioScience Trends* takes seriously all allegations of potential misconduct and adhere to the ICMJE Guideline (*https://icmje.org/recommendations*) and COPE Guideline (*https://publicationethics.org/files/Code_of_conduct_for_journal_editors.pdf*). In cases of suspected research or publication misconduct, it may be necessary for the Editor or Publisher to contact and share submission details with third parties including authors' institutions and ethics committees. The corrections, retractions, or editorial expressions of concern will be performed in line with above guidelines.

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