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EDITORIAL

Current strategies for predicting post-hepatectomy liver failure and a new ultrasound-based nomogram

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Abstract

Liver cancer is associated with a few factors, such as viruses and alcohol consumption, and hepatectomy is an important treatment for patients with liver cancer. However, post-hepatectomy liver failure (PHLF) is the most serious complication and has a high mortality rate. Effective prediction of PHLF allows for the adjustment of clinical treatment strategies and is critical to the long-term prognosis of patients. Many factors have been associated with the development of PHLF, so there is an increasing interest in the development of predictive models for PHLF, such as nomograms that integrate intra-operative factors, imaging and biochemical characteristics of the patient. Ultrasound, as a simple and important examination method, plays an important role in predicting PHLF, especially the Nomogram established based on ultrasound measurements of liver stiffness and spleen area provides a more convenient way to predict the occurrence of PHLF.

Key Words: Ultrasound; Liver stiffness; Spleen area; Hepatocellular carcinoma; Post-hepatectomy liver failure

Core Tip: Existing strategies for predicting post-hepatectomy liver failure include multiple clinical scoring systems that assess surgical risk by quantifying metrics related to liver function. However, each has limitations such as high subjectivity and insufficient prediction accuracy. Ultrasound-based nomograms are innovative predictive methods that combine radiomic features with clinical risk factors and construct a model through multivariate logistic regression to achieve prediction of post-hepatectomy liver failure. This method is non-invasive, low cost and high precision, and is expected to provide clinicians with a more reliable prediction tool, assisting doctors in formulating optimal surgical and therapeutic plans.

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INTRODUCTION

Liver cancer is the fifth most common malignancy and the second leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) accounting for 75%-85% of all liver cancers[1]. Hepatic resection is an important treatment for patients with liver cancer to achieve long-term survival, especially in those with good hepatic reserve function and early stage tumors. The safety of hepatic resection has improved significantly in recent years, but the morbidity and mortality rates after hepatic resection remains high, ranging from 4.09% to 47.7% and 0.24% to 9.7%, respectively. Post-hepatectomy liver failure (PHLF) is one of the most serious post-operative complications and a major cause of death, usually occurring within 5 days after surgery[2], with an incidence of 0.7% to 34%[3]. PHLF is attributed to various etiologies, patients' physiological conditions, and surgery-related factors, posing a challenge to clinicians and patients. Therefore, the accurate prediction of the PHLF is of utmost importance. Various available prediction models based on patient clinical data, pre-operative liver function, and imaging characteristics provide strong support for clinical decision-making, significantly reducing surgical risk, optimizing patient management, and improving patient prognosis.

CURRENTLY AVAILABLE PREDICTIVE MODELS

Serological markers

Infection markers are also associated with PHLF occurrence. Procalcitonin levels correlate with long- and short-term prognoses after surgery and are an early diagnostic indicator of post-operative outcomes. After hepatectomy, elevated procalcitonin levels are significantly associated with PHLF and poor short-term prognosis and may be useful biomarkers for predicting patient prognosis[4]. Accelerated intrahepatic neutrophil infiltration and neutrophil extracellular traps formation are linked with liver damage and PHLF. Myeloperoxidase, a circulating marker of neutrophil extracellular trap formation, helps identify patients at higher risk of PHLF for individualized treatment[5].

Lactate is sensitive to intra-operative bleeding events, and lactate levels within 24 hours after surgery are effectively in predicting liver prognosis[6]. However, factors limiting liver function, such as liver volume, also affect post-operative serum lactate levels. Although strongly influenced by cardiac and pulmonary diseases, lactate levels predict PHLF poorly. Lysophospholipase D is an autotoxin and a potential marker of liver fibrosis. This enzyme catalyzes the hydrolysis of lysophosphatidylcholine to lysophosphatidic acid, which in turn activates hepatic stellate cells and stimulates hepatic fibrosis[7]. Liver stiffness (LS) can predict PHLF[8], and serum autotaxin levels are related to the degree of liver fibrosis caused by various etiologies, with less influence from diabetes and chronic kidney disease, making it a potential biomarker for predicting PHLF[7]. However, their clinical applications are not widespread.

Alanine aminotransferase, total bilirubin, platelet counts, and prealbumin levels are also independent risk factors for PHLF[1,3]. Patients with platelet counts ≤ 145 × 10^9/L are at a high risk of PHLF[9]. Conclusively, various serum markers reflect the functional status and degree of liver injury from different perspectives and can potentially predict PHLF. However, their sensitivity and specificity and specific applications differ and are influenced by multiple factors. Combining different serum markers for PHLF risk assessment during clinical events can improve the predictive value of serum markers to further optimize clinical management and improve treatment outcomes.

Scoring system

The albumin-bilirubin (ALBI) score, aspartate aminotransferase/platelet ratio index (APRI), model for end-stage liver disease (MELD), and Child-Pugh score are commonly used scoring systems for assessing the condition of patients with liver disease and hepatic reserve function. PHLF is categorized into three grades (A, B, and C) based on severity, with grades B and C indicating severe PHLF. ALBI grade 2/3 is a stronger predictor of severe PHLF than MELD ≥ 10[10], demonstrating an increased risk of severe PHLF for every 1-point increase in the ALBI score[11]. Fibrosis-4 is a noninvasive method for assessing liver fibrosis and is an independent risk factor for PHLF. The combination of ALBI score with fibrosis-4 predicted PHLF with an area under the receiver operating characteristic curve (AUC) of 0.783, which was higher than that of the other scores. The patients were divided into two risk groups of high and low risks according

to a cutoff value of -1.82. The incidence of PHLF in high-risk and low-risk patients was 39.1% and 6.6%, respectively, which has a good application value. However, the accuracy of the cutoff value still needs further verification[12]. The maximum liver function capacity test is a dynamic liver function test that evaluates the residual functional capacity of the liver and has a strong predictive ability for PHLF. However, the predictive efficacy of the combined APRI and ALBI scores was higher for predicting severe PHLF and mortality[13]. Overall, the PHLF predictive ability of a combination of multiple scores was superior to that of a single score.

A combination of scoring systems, intra-operative factors, and post-operative indicators predicted PHLF with high accuracy. Pre-operative ALBI grade, Child-Pugh classification, international normalized ratio, cirrhosis, and intra-operative blood loss were independently associated with severe PHLF. The predictive accuracy of the nomogram with an AUC ≥ 0.74 constructed based on these five factors was higher than that of the ALBI and Child-Pugh scores[14]. In addition, the APRI score, MELD score, operative time, and intraoperative bleeding were significantly associated with PHLF severity. These factors established a new scoring model for each patient as follows: APRI ≥ 1.56, MELD ≥ 8.3, operative time ≥ 407 minutes, and blood loss ≥ 847 mL were scored as 1 point each. A total score of 0, 1-2, and 3-4 indicated a low, medium, and high risk, respectively[15]. The model with a clear cutoff value that integrates intra-operative factors may have a higher predictive accuracy than a model based on single score. However, pre-operative factors remain unassessed, and the cutoff value requires further validation.

Imaging technology

Computed tomography (CT)-derived extracellular volume is commonly used to assess the size of the extracellular volume in organs or tissues and is an independent risk factor for PHLF. Compared with the Child-Pugh, MELD, and ALBI scores, nomograms combining CT-derived extracellular volume, serum albumin, and serum total bile acids were better predictors of PHLF, with an AUC of 0.828[16]. Combined with the future liver remnant ratio and serum albumin level, the predictive power was also superior to the ALBI score[17]. Spleen volume is associated with PHLF, and PHLF occurs in patients with HCC with a larger spleen volume[18]. The AUC for predicting PHLF by combining the CT-measured spleen volume with the liver-to-spleen signal intensity ratio measured by EOB- EOB-magnetic resonance imaging (MRI) and serum hyaluronic acid was 0.91, indicating high accuracy[19].

The overall and local liver function can be assessed using MRI. A reduced residual hepatocyte uptake index on gadoxetic acid-enhanced MRI is an independent risk factor for PHLF and significantly correlated with PHLF severity[20]. MRI can reveal the radiomic characteristics of the liver tissue, which reflect the characteristics of non-tumorigenic areas under tumor influence. Platelet count and tumor size were independent risk factors for PHLF. Radiomics scores combined with platelet count and tumor size can effectively predict PHLF[21]. The functional status of the liver can be assessed by MRI measurements of the quantitative liver-to-portal vein and liver-spleen contrast ratios. These are independent risk factors for PHLF development, with AUCs of 0.882 and 0.782 for predicting PHLF grades B-C, respectively[22], which can effectively assist in the clinical prediction of PHLF risk. Although MRI and CT have a certain value in predicting the occurrence of PHLF, multiple factors, including pre-operative hepatic function status, surgical scope, intra-operative blood loss, and post-operative management, affect PHLF. Therefore, PHLF risk assessment should consider these other factors to improve the accuracy and reliability of PHLF predictions.

Other relevant factors

Muscularity, defined by muscle quantity and quality, may accelerate hepatic regeneration or functional reversal. In patients with primary HCC, low muscularity is an independent risk factor for PHLF and is associated with severe PHLF development[23]. Major hepatic resection was associated with a higher risk of PHLF when the residual/total liver volume was ≤ 0.56 and a lower risk of PHLF when the residual/total liver volume was ≥ 0.6[9,24]. Patients > 75-years have increased risk of developing PHLF after right hepatectomy, contributing to increased mortality and economic burden [25]. In addition, post-operative complications, such as infectious pneumonia, sepsis, blood transfusion, and infectious shock, have been associated with the development of PHLF. Patients with these diseases have a 2-to-3-fold increased risk of developing PHLF[26]. Careful assessment of the patient's residual liver volume, nutritional status, and timely management of post-operative infections can reduce the incidence and mortality of PHLF and are important for optimizing treatment strategies and improving patient outcomes.

In addition, the unresected liver tissue after HCC resection may compensate for the lost liver volume through compensatory proliferation. However, various factors, including the volume of the resected liver, patient's age, degree of liver fibrosis, and the presence of other complications, influence liver regeneration. In addition, patients with the same residual liver volume may have significantly different liver functional reserves depending on factors such as the degree of fibrosis or altered portal circulation. Portal hypertension and portal vein obstruction time > 30 minutes are risk factors for PHLF[4], and patients with hepatic venous pressure gradient ≥ 10 mmHg have a significantly increased risk of PHLF[27]. The initially similar post-operative residual liver volume may change later because of the patients' different hepatic functional reserves and baseline conditions, which in turn affects the short-term and long-term post-operative prognosis. Therefore, the dynamic changes in predictors that reflect the residual liver volume and functional status of hepatocytes necessitate further attention.

ULTRASOUND IN PREDICTING PHLF

Liver resection volume in patients with HCC is associated with PHLF. Accurate assessment of the residual liver volume is critical. Clinicians tend to overestimate the residual liver volume, especially in patients with a small residual liver

volume, in whom the risk of post-operative PHLF is greatest[28]. The three-dimensional reconstruction of the liver and its vascular system by collecting patient CT data and using three-dimensional simulation software allows for the visualization of the liver, bile ducts, tumors, and blood vessels in relation to each other. Three-dimensional imaging and intraoperative ultrasound offer significant advantages in calculating liver volume and have been widely used for hepatectomy risk assessment[24].

Two-dimensional ultrasound shear wave elastography is an important method for assessing the stiffness of human tissues. LS can be detected using two-dimensional ultrasound shear wave elastography. Elevated LS levels are associated with PHLF, and LS ≥ 9.5 kPa is an independent risk factor for severe PHLF[29]. The sensitivity for predicting ≥ PHLF A was 86.1% at a LS cutoff value of 8.45 kPa; the specificity for predicting ≥ PHLF B increased to 71.2% at a cutoff value of 12.70 kPa; and the sensitivity and specificity for predicting ≥ PHLF C were both > 80.0% at a cutoff value of 14.90 kPa, indicating that for patients with pre-operative LS higher than 14.9 kPa, their surgery plan might be reconsidered to avoid PHLF C[30]. Despite the many advantages of two-dimensional ultrasound shear wave elastography, such as real-time elastography, non-invasiveness, and reproducibility, specific factors still affect its diagnostic efficacy, such as the patient's alanine aminotransferase level, obesity, and breath-holding ability. Combining LS with patients' clinical characteristics allows for a more accurate prediction of post-operative events.

Ultrasound plays a role in predicting the occurrence of PHLF mainly by measuring LS values, liver and spleen volumes, and constructing nomograms based on these in combination with pre-operative and intra-operative relevant factors. In the article published in a recent issue of *World Journal of Gastroenterology* by Cheng *et al*[31], titled "Nomogram based on liver stiffness and spleen area with ultrasound for posthepatectomy liver failure: A multicenter study", LS and spleen area were measured by ultrasound in 562 patients, and blood was drawn to assess liver function and other conditions within one week before partial hepatectomy[31]. Independent predictors of PHLF were identified and a nomogram was developed. The diagnostic performance of the nomogram was evaluated with receiver operating characteristic curve and compared with the conventional models, including MELD score and ALBI score. The study had two main findings. First, LS and spleen area were found to be independent risk factors for severe PHLF. Patients with LS ≥ 12.52 kPa had an increased risk of severe PHLF with an AUC of 0.8 and a diagnostic efficacy superior to that of the MELD score and ALBI score. Second, patients were grouped for major and minor hepatectomy. LS and spleen area were assessed using the following dual cutoff diagnosis: For LS, 10.34 kPa in the major liver resection group (AUC = 0.74) and 13.48 kPa in the minor liver resection group (AUC = 0.78); for spleen area: 33.7 cm^2 in the major liver resection group (AUC = 0.78) and 43.2 cm^2 in the minor liver resection group (AUC = 0.84). Subgroup analyses of different conditions are important to provide surgeons with diagnostic cutoff values for different clinical situations.

However, this study had several limitations. First, liver function is dynamic, and various factors are associated with post-operative liver function, such as abdominal infection and portal hypertension, especially in some patients with HCC who already have pre-operative cirrhosis and are at a relatively high risk of developing post-operative portal hypertension. In this study, the pre-operative and intra-operative factors associated with the occurrence of PHLF were analyzed, and the inclusion of post-operative factors improved the value of the study. Second, this study provides a clear LS cut-off value; however, ultrasound shear wave elastography measurement of the LS value is affected by various factors, such as the patient's intestinal lumen pneumatization and cholestasis, which may lead to obstruction of the propagation of the sound wave in the liver tissues, or introduce bias, which affects the accuracy of the LS value. In addition, the measurement of LS values may differ between different brands and models of ultrasound instruments. The examiner's operating technique and probe placement position may also have affected the LS measurement results. Therefore, the applicability of the cutoff values requires further validation.

Many studies have developed predictive models for PHLF risk based on ultrasound-measured LS values with different cutoff values. Possible reasons for the different cut-offs may be the different sample sizes in different studies and the fact that a few factors influence the measurement of LS, including liver inflammation, examination techniques, and equipment. HCC differs in its biological properties, tissue structure, and pathological changes due to different etiologies. Most studies did not analyze the etiology in the subgroups, which may have led to different cutoff values for LS. Future subgrouping of etiologies is needed in larger studies. Overall, ultrasound is a convenient detection method. The risk of PHLF was predicted for the first time in this study by combining the LS and spleen areas and providing a clear cut-off value, thereby greatly simplifying the pre-operative PHLF risk assessment. However, the accuracy of the cutoff values needs to be verified in future research and practice.

CONCLUSION

Ultrasound is noninvasive, real-time, highly accurate, and easy to perform for predicting PHLF. Nomograms constructed based on ultrasound-measured LS values and spleen area are a relatively new and simple method for assessing PHLF risk, which can help optimize treatment plans and perioperative management and improve patient prognosis and quality of life. Prediction tools for PHLF are constantly being improved and developed, ranging from clinical scoring systems to imaging techniques as well as biochemical indicators and other testing methods, all of which provide strong support for a more accurate prediction of PHLF. Future models for predicting PHLF will move towards precision, personalization, multimodality, real-time dynamics, and intelligent-assisted decision-making. These advances have provided clinicians with comprehensive, accurate, and reliable predictive information.

FOOTNOTES

Author contributions: Gao XX and Li JF contributed to this paper; Gao XX wrote and revise the manuscript; Li JF review and revise the manuscript.

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