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Retrospective Study

Prediction of hepatic artery occlusion after liver transplantation by ultrasound characteristics and clinical risk factors

Yu-Ting Lai, Yi Chen, Tai-Shi Fang, Zhi-Yan Li, Ning-Bo Zhao

Specialty type: Radiology, nuclear medicine and medical imaging**Provenance and peer review:**

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Hepatic artery occlusion (HAO) after liver transplantation (LT) is a devastating complication, resulting in early graft loss and reduced overall survival. Ultrasound is an established assessment method for HAO in patients following LT, especially those with complex hepatic artery reconstruction.

AIM

To investigate the ultrasound characteristics and analyze the risk factors associated with HAO in patients after LT.

METHODS

We retrospectively analyzed the ultrasound characteristics and the clinic risk factors associated with HAO in 400 adult LT patients who were enrolled and treated at the Third People's Hospital of Shenzhen between November 2016 and July 2022. Fourteen patients diagnosed with acute HAO (A-HAO) by surgery and fifteen diagnosed with chronic HAO (C-HAO) were included. A control group of 33 patients without HAO complications during the same period were randomly selected using a random number table. All patients underwent an ultrasono-

graphy examination. Parameters including resistance index (RI), peak systolic velocity (PSV), and portal vein velocity (PVV) were compared across the groups. Additionally, basic clinical data were collected for all patients, including gender, age, primary diagnosis, D-dimer concentration, total operation time, cold ischemia time, hot ischemia time, intraoperative blood loss and transfusion, intraoperative urine volume, infusion, model for end-stage liver disease (MELD) score, and whether complex hepatic artery reconstructions were performed. Furthermore, risk factors influencing HAO formation after LT were analyzed.

RESULTS

Compared to the non-HAO group, PVV and RI were higher in the A-HAO group, while PSV was lower. Conversely, both PSV and RI were lower in the C-HAO group compared to the non-HAO group. The proportion of patients undergoing complex hepatic artery reconstructions and the gamma-glutamyltransferase (GGT) level before occlusion were significantly higher in the A-HAO group compared to the non-HAO group. However, there were no distinct differences between the two groups in D-dimer, MELD score, pre-occlusion alanine transaminase and aspartate transaminase levels, or intraoperative conditions.

CONCLUSION

Ultrasound features of the hepatic artery before occlusion are significantly associated with postoperative HAO development. Additionally, complex hepatic artery reconstructions, defined as revascularization of the graft requiring additional anastomosis between donor hepatic arteries, constitute a risk factor for A-HAO. Besides, abnormal pre-occlusion GGT elevation is an important biochemical indicator. Therefore, ultrasound examination serves as an important tool for screening HAO, especially in patients with the identified risk factors.

Key Words: Hepatic artery occlusion; Ultrasonography; Diagnostic performance; Risk factors; Liver transplantation

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Core Tip: This research investigated the related risk factors and ultrasound features of hepatic artery occlusion (HAO) following liver transplantation. It highlighted that ultrasound measure parameters, such as resistance index, peak systolic velocity, and portal vein velocity, could effectively predict the development of HAO. Furthermore, clinical risk factors, including complex hepatic artery reconstruction, high gamma-glutamyltransferase level, and so on, also increased HAO occurrence. These findings highlight the key role of selecting and increasing the frequency of ultrasound monitoring to mitigate risk and optimize prognosis, offering valuable insights for clinicians in managing this complex complication effectively.

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INTRODUCTION

Hepatic artery occlusion (HAO) after liver transplantation (LT) is a devastating complication, resulting in early graft loss and reduced overall survival. HAO typically develops from hepatic artery (HA) stenosis and thrombosis. Traditionally, HAO is divided into acute HAO (A-HAO, occurring within 1 mo) and chronic HAO (C-HAO, occurring 1 mo or later after LT)[1]. HAO can progress to ischemic bile duct necrosis with or without hematosepsis, early graft failure, or even mortality[2]. Although collateral circulation may develop in C-HAO, liver damage remains significant. Hence, early detection and timely management, especially for A-HAO, are crucial for a favorable outcome in LT recipients. Color Doppler ultrasound, with its simplicity, non-invasiveness, and repeatability, can be used as a routine screening method for LT recipients to assess the degree of stenosis and thrombosis. Predicting the occurrence of HAO through ultrasound features and associated risk factors is crucial in clinical practice, particularly since A-HAO can develop rapidly within hours. While many risk factors for HAO have been reported[3-6], some remain controversial. This study aimed to investigate whether ultrasonic imaging features and high-risk factors of HAO before occlusion could predict and diagnose HAO.

MATERIALS AND METHODS

Patient characteristics and methods

Between November 2016 and July 2022, 400 LTs were performed at The Third People's Hospital of Shenzhen. Fourteen recipients (13 males and 1 female), with a mean age of 44.1 years \pm 11.9 years, were diagnosed with A-HAO confirmed by surgery. The mean time for these individuals to develop HA stenosis after LT was 2.5 d. Patients were included in the HAO group if they met the following criteria: Underwent LT, developed HAO within 1 mo confirmed by both contrast-enhanced ultrasound (CEUS) and X-ray micro-computed tomography angiography (CTA), and had a surgical diagnosis of A-HAO. Similarly, 15 recipients (14 males and 1 female), with a mean age of 46.4 years \pm 12.3 years, were diagnosed with C-HAO, met the inclusion criteria including the occurrence of HAO after 1 mo following LT, and were confirmed *via* CEUS or CTA. From the remaining patients without any hepatic artery complications, 32 were randomly selected as the non-HAO group using a random number table. They had a mean age of 52.2 years \pm 11.5 years (27 males and 6 females). This study evaluated ultrasound features [resistance index (RI), peak systolic velocity (PSV), and portal vein (PV) velocity (PVV)] of LT patients before HA occlusion, comparing them to the lowest values observed in the non-HAO group. Additionally, the following clinical data were collected for both groups: Gender, age, tumor history, D-dimer concentration, total operation time, cold ischemia time, hot ischemia time, intraoperative bleeding, blood transfusion, intraoperative urine volume, total infusion volume, model for end-stage liver disease (MELD) score, complex hepatic artery reconstructions[7,8], and liver enzyme levels [alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyltransferase (GGT)].

Instruments and methods

During the liver transplant process, within 24 h afterward, and daily for the first week, ultrasound examinations were conducted using a Mindray Resona 7T and M9 ultrasound diagnostic instrument equipped with a 1.5 MHz-6.0 MHz transducer. These examinations continued four times per month for the first month after surgery, with the option for additional examinations based on the patient's condition.

Following established criteria, measurements were taken at specific locations: The proper hepatic artery, right and left hepatic arteries, and intrahepatic arteries. These measurements were obtained at the artery anastomosis near the right hepatic artery, the right anterior branch of the PV, the sagittal part of the PV, and the left or right main hepatic artery, respectively. Ensuring that the ultrasonic sound beam paralleled the measured hepatic artery, parameters like RI and PSV were measured three times and averaged.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 25.0 for Windows, Inc., Chicago, IL, United States). Data with a normal distribution were compared using the Student's *t*-test and are presented as the mean \pm SD. Non-normally distributed data were analyzed using the Mann-Whitney *U* test (rank-sum test) and are presented as median and interquartile range [M (P25, P75)]. Categorical variables were analyzed using the chi-square test and are presented as percentages or frequency ratios. Multivariate logistic regression was employed to identify risk factors for HAO. A separate logistic regression model was constructed including sex, age, MELD score, and D-dimer concentration as predictors. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of different groups

The A-HAO group presented with a significantly higher proportion of complex hepatic artery reconstructions and higher GGT levels before artery occlusion compared with the non-HAO group ($P < 0.05$). However, other parameters, including D-dimer, MELD score, and pre-occlusion ALT and AST, showed no significant differences between the two groups. Similarly, no significant differences were observed in various intraoperative indices between the two groups (Table 1).

Ultrasound features of different groups

The A-HAO group demonstrated a significantly higher level of left PV (L-PV) compared to the control group, with no significant differences observed in the right PV (R-PV) and main PV. Additionally, the A-HAO group exhibited significantly lower pre-occlusive hepatic artery PSV and both left and right hepatic artery PSV before occlusion compared to the control group. Conversely, the RI was significantly higher in the A-HAO group compared to the control group (Figure 1 and Table 2).

Immediate postoperative ultrasound (Figure 1A) showed the right HA with low velocity and high resistance. Digital subtraction angiography performed on the second postoperative day showed both the hepatic proper artery and the left and right branches to be invisible (Figure 1B). White arrows indicate the hepatic arteries not filled with contrast material.

The pre-occlusion values of PSV and resistance index in the hepatic artery, left hepatic artery, and right hepatic artery were significantly lower in the C-HAO group compared to the control group (Figure 2 and Table 2).

After 5 mo, an ultrasound examination (Figure 1A) revealed low velocity and resistance in the left HA. A subsequent CTA demonstrated non-visualization of the hepatic propria artery (indicated by white arrow in Figure 2A), suggesting complete occlusion. Additionally, the development of peripheral collateral circulation was evident (indicated by orange arrow in Figure 2B).

Table 1 Summary of sociodemographic characteristics and intraoperative situation of both groups

	Non-HAO	A-HAO	P value	C-HAO	P value
Sex			0.66		0.41
Female	6 (18.18)	1 (7.14)		1 (6.67)	
Male	27 (81.82)	13 (92.86)		14 (93.33)	
Age, yr	52.2 ± 11.5	44.1 ± 11.9	0.04	46.4 ± 12.3	0.12
HAR			0.01		0.58
N	31 (93.94)	8 (57.14)		13 (86.67)	
Y	2 (6.06)	6 (42.86)		2 (13.33)	
MELD score	23.7 ± 11.3	19.5 ± 10.9	0.25	26.7 ± 10.3	0.37
ALT (D-1)	33.00 (25.00, 175.76)	44.00 (30.25, 90.07)	0.45	21.00 (15.00, 35.53)	0.2
AST (D-1)	69.00 (37.00, 348.85)	52.50 (45.50, 70.86)	0.15	22.00 (17.00, 29.60)	0.09
GGT (D-1)	48.00 (38.00, 72.55)	93.50 (48.50, 122.71)	0.02	43.00 (33.50, 99.73)	0.33
D-dimer	3.09 (1.24, 5.70)	5.01 (2.27, 5.76)	0.97	1.22 (0.46, 1.30)	< 0.01
		2.5 (1.0, 6.6)		153.0 (92.0, 325.7)	
Intraoperative variables					
Cold ischemic time (h)	6.00 (5.00, 5.94)	5.60 (5.00, 5.80)	0.75	5.00 (4.00, 5.69)	0.64
Total operative time (h)	8.15 (7.62, 8.72)	9.25 (8.27, 9.40)	0.38	8.67 (7.67, 9.17)	0.52
Hepatic phase (min)	40.00 (36.00, 43.09)	40.00 (32.75, 41.79)	0.71	37.00 (36.00, 40.53)	0.45
Frozen plasma (mL)	1300 (1000, 1353)	1400 (962, 1507)	0.44	1400 (1350, 1460)	0.50
Intraoperative urine output (mL)	1350 (575, 1612)	1500 (725, 1361)	0.51	1800 (500, 1909)	0.50
Total amount of infusion (mL)	4525 (3550, 5124)	5625 (4984, 5734)	0.34	6150 (4050, 5957)	0.24
Intraoperative bleeding (mL)	1000 (800, 1548)	1125 (500, 2282)	0.18	1500 (700, 2160)	0.29

Data are presented as the mean ± SD, with the range of values shown in parentheses. The non-hepatic artery occlusion (HAO) group comprised patients without any hepatic artery complications after liver transplantation. The acute HAO (A-HAO) and chronic HAO (C-HAO) groups included patients with either complete HAO or significant stenosis causing complications. $P < 0.05$ was considered statistically significant. MELD: Model for end-stage liver disease; HAR: Hepatic artery reconstructions; HAO: Hepatic artery occlusion; GGT: Gamma-glutamyltransferase; N: No reconstruction; Y: Reconstruction performed; ALT: Alanine aminotransferase; AST: Aspartate transaminase; D-1: The day before arterial occlusion.

DISCUSSION

HAO is a recognized risk factor for graft survival following LT[9]. Therefore, early diagnosis and preventative measures are crucial for successful management. Complex hepatic artery reconstruction is indicated when encountering significant anatomical variations in the donor's hepatic artery or specific recipient hepatic artery lesions. Wu *et al*[10] have demonstrably linked complex arterial reconstruction to an increased risk of hepatic artery thrombosis, consequently raising the potential for postoperative arterial complications. This study further revealed a significantly higher proportion of patients with complex hepatic artery reconstructions in the A-HAO group compared to the control group. Accordingly, ultrasound can be implemented as a first-line approach for both evaluation and monitoring of HAO in LT patients who undergo complex hepatic artery reconstructions[11,12].

Our findings demonstrated that, in the A-HAO group, pre-occlusion levels of both RI and PVV were significantly higher compared to those of the non-HAO group. Conversely, pre-occlusion PSV of the hepatic artery was lower in the A-HAO group. The observed elevation in PVV in the A-HAO group might contribute to a short-term self-regulatory mechanism by the liver during ischemic episodes. Furthermore, this study suggests that L-PVV is more responsive to adaptive and compensatory increases in hepatic blood flow. This phenomenon is likely attributable to the distinct anatomical positioning of the left and right PV branches. Additionally, PSV and RI serve as crucial indicators for the evaluation of A-HAO. A decrease in PSV alongside a higher RI suggests a reduction in hepatic perfusion[12], potentially culminating in an increased risk of arterial thrombosis and ultimately leading to the development of A-HAO.

Prior research has established that occlusion of the C-HAO can be accompanied by the development of collateral arteries within a timeframe ranging from 2-3 mo to even longer durations[13]. However, these collateral vessels are typically characterized by small size, with a maximum diameter rarely exceeding 3 mm, and are additionally prone to occlusion as demonstrated in most studies. Consequently, the presence or absence of adequate hepatic arterial collateral

Table 2 Description of ultrasound features in different groups

Imaging marker	Non-HAO	A-HAO	P value	C-HAO	P value
L-PV (cm/s)	24.00 (19.00, 23.42)	29.00 (19.25, 34.86)	0.01	21.00 (13.50, 23.07)	0.06
R-PV (cm/s)	31.00 (24.00, 34.82)	38.50 (27.25, 40.86)	0.21	27.00 (20.00, 36.87)	0.73
PV (cm/s)	42.00 (28.00, 53.42)	58.00 (49.75, 59.00)	0.57	32.00 (26.50, 39.20)	0.14
PSV of pre-occlusion HA	84.00 (68.00, 91.61)	38.00 (17.25, 50.79)	< 0.01	42.00 (18.00, 58.01)	< 0.01
RI of pre-occlusion HA	0.66 (0.64, 0.66)	0.92 (0.70, 0.82)	< 0.01	0.60 (0.53, 0.56)	< 0.01
PSV of pre-occlusion LHA	47.00 (34.00, 50.12)	19.00 (12.00, 23.71)	< 0.01	23.00 (14.50, 23.07)	< 0.01
RI of pre-occlusion LHA	0.58 (0.53, 0.57)	1.00 (0.53, 0.77)	< 0.01	0.42 (0.39, 0.44)	< 0.01
PSV of pre-occlusion RHA	45.00 (37.00, 48.03)	21.50 (13.00, 25.29)	< 0.01	25.00 (17.00, 25.53)	< 0.01
RI of pre-occlusion RHA	0.59 (0.56, 0.58)	1.00 (0.48, 0.78)	< 0.01	0.40 (0.38, 0.41)	< 0.01

Data are presented as the mean \pm SD, with the range of values shown in parentheses. $P < 0.05$ was considered statistically significant. L-PV: Left portal vein; R-PV: Right portal vein; PV: Portal vein; PSV: Peak systolic velocity; RI: Resistance index; HA: Hepatic artery; LHA: Left hepatic artery; RHA: Right hepatic artery.



Figure 1 A 46-year-old male patient with hepatic malignant tumors in cirrhosis underwent liver transplantation surgery. A: Postoperative ultrasound; B: Digital subtraction angiography. White arrows indicate the hepatic arteries not filled with contrast material.

circulation significantly influences patient prognosis following LT[14]. A previous study reported that 41.7% of patients with C-HAO occlusion and established collateral circulation still experience symptoms associated with hepatic ischemia [15]. This finding underscores the critical importance of early intervention in clinical settings. Therefore, a decrease in PSV and RI following LT should serve as a warning sign for potential C-HAO.

Following LT, the hepatic artery serves as the primary source of blood supply to the extrahepatic bile ducts during the initial postoperative period. Due to its extensive distribution within the liver's bile duct system, GGT is frequently employed as a biomarker to aid in the diagnosis of hepatobiliary diseases[16]. Our study revealed significantly elevated GGT levels in the A-HAO group compared to the control group prior to occlusion. This finding suggests a high degree of sensitivity for GGT in detecting biliary ischemia[17] and a strong correlation between abnormally elevated GGT levels and A-HAO. Furthermore, serum GGT is recognized as a prognostic factor for HCC patients who have undergone LT [18]. It is noteworthy that abnormal or progressively increasing GGT levels following LT are highly suggestive of vascular complications, particularly the development of A-HAO.

In our study, no significant difference in D-dimer levels was observed between the A-HAO and non-HAO groups, which may be attributed to the routine use of prophylactic anticoagulants during the early postoperative period, potentially masking potential elevations associated with A-HAO. Conversely, the C-HAO group exhibited lower D-dimer levels compared to the control group. This finding might be related to the prolonged use of anticoagulants in these patients, potentially suppressing D-dimer production despite ongoing low-grade thrombosis.

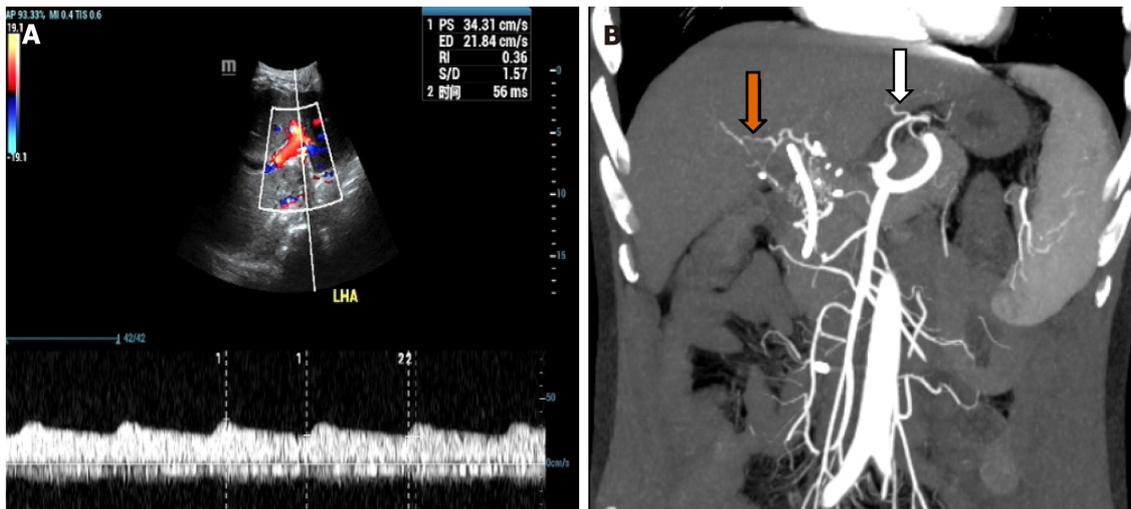


Figure 2 A 52-year-old male patient with cirrhosis due to hepatic malignant tumors underwent liver transplantation surgery. A: X-ray micro-computed tomography angiography; B: Peripheral collateral circulation. LHA: Left hepatic artery.

This study is subject to several limitations. First, inherent limitations associated with the early post-transplantation period can hinder accurate ultrasound evaluation. These limitations include: Anastomotic edema, transplanted liver swelling, narrow hepatic artery diameter, and variability in examination technique between operators. All these factors can complicate visualization of the hepatic artery and potentially lead to false positive diagnoses. Second, the study design presented a challenge in obtaining statistically significant results for R-PV flow rate. This can be attributed to the often narrow angle between the R-PV and the main PV, making it difficult to consistently align the ultrasound beam with the direction of blood flow in this vessel. Finally, the generalizability of these findings is limited due to the relatively small sample size employed in the study. Validation of the clinical value of this approach requires further investigation through large-scale, multicenter clinical trials.

CONCLUSION

In conclusion, color Doppler ultrasound, due to its non-invasive and real-time nature, stands as the primary modality for monitoring vascular complications following LT and assessing liver blood perfusion[19,20]. Our findings provide compelling evidence that patients with complex vascular reconstruction, along with abnormally elevated serum GGT levels and increased PVV and RI, warrant close monitoring for the potential development of acute HAO. Similarly, vigilance for C-HAO is essential when intrahepatic arteries exhibit characteristics such as small, slow waveforms, low velocity, and low resistance. Therefore, it becomes crucial to appropriately increase the frequency of ultrasound monitoring and consider the implementation of CEUS for a more definitive assessment.

FOOTNOTES

Author contributions: Lai YT and Chen Y contributed equally to this work; Lai YT designed and preformed the research study; Chen Y collected the primary data and wrote the manuscript; Fang TS sorted the reference literature; Li ZY and Zhao NB were responsible for supervising the study and revising the manuscript; and all authors read and approved the final version.

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