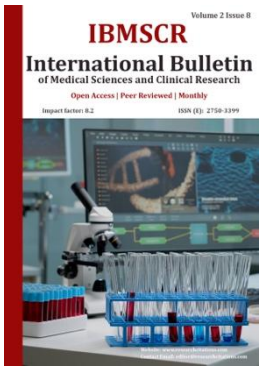

HEPATIC ARTERY THROMBOSIS AFTER LIVER TRANSPLANTATION: RISK FACTORS, EARLY DIAGNOSIS AND CONTEMPORARY TREATMENT STRATEGIES

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Abstract; The liver is one of the largest internal organs in the human body. The liver is involved in numerous vital processes, including metabolism, detoxification, protein synthesis, immune defense, energy storage, and bile production. Severe and irreversible impairment of liver function may result in multiorgan failure. In patients with end-stage liver disease, liver transplantation is one of the principal life-saving treatment options. However, various vascular complications may develop during the post-transplant period, including hepatic artery thrombosis (HAT). Hepatic artery thrombosis compromises the arterial blood supply of the liver graft and may cause severe ischemic injury, particularly to the biliary tract, potentially resulting in graft loss. This review discusses the anatomical and physiological characteristics of the liver, its blood supply, the principal aspects of liver transplantation, as well as the risk factors, pathogenesis, clinical manifestations, early diagnosis, and contemporary treatment strategies for hepatic artery thrombosis.

Keywords: liver, liver function, hepatic circulation, liver transplantation, hepatic artery, hepatic artery thrombosis (HAT), Doppler ultrasonography, angiography, thrombectomy, revascularization.

Introduction; The liver is the largest parenchymal organ in the human body and is located in the right upper quadrant of the abdominal cavity, beneath the diaphragm. It has a complex anatomical structure consisting of the right and left lobes, as well as the quadrate and caudate lobes. In adults, the liver accounts for approximately 2% of total body weight. Its mass varies depending on sex, age, body habitus, and physiological status. The liver is a highly vascularized organ and receives a substantial proportion of the cardiac output. One of its distinctive characteristics is its dual blood supply: the majority of hepatic blood flow is provided by the portal vein, while the remainder is supplied by the hepatic artery.

The portal vein carries venous blood rich in nutrients and metabolites from the intestines, pancreas, and spleen to the liver. The hepatic artery, in contrast, supplies oxygen-rich arterial blood. Under normal conditions, approximately 70–75% of hepatic blood flow is derived from the portal vein, while 25–30% is supplied by the hepatic artery. These two blood streams mix within the hepatic sinusoids and subsequently drain through the central veins into the hepatic veins and then into the inferior vena cava. The dual blood supply of the liver is of major physiological importance. Blood delivered through the portal vein supplies the liver with glucose, amino acids, fatty acids, vitamins, and other substances absorbed from the gastrointestinal tract. The hepatic artery plays a particularly important role in maintaining

adequate oxygenation. In addition, the blood supply of the biliary tract is predominantly dependent on arterial blood flow. Therefore, abrupt cessation of hepatic arterial flow is particularly dangerous in the setting of liver transplantation.

The liver participates in hundreds of biochemical and physiological processes throughout the body. One of its principal functions is the regulation of metabolism. In carbohydrate metabolism, the liver plays a crucial role in maintaining stable blood glucose concentrations. It also has a central role in protein metabolism. Albumin, fibrinogen, and many coagulation factors are synthesized in the liver. Albumin is essential for maintaining plasma oncotic pressure and transporting various substances. Severe impairment of liver function may reduce albumin synthesis, resulting in peripheral edema and the accumulation of fluid within the abdominal cavity, known as ascites. Reduced synthesis of coagulation factors increases the tendency to bleeding. The liver is also actively involved in lipid metabolism, including fatty acid oxidation, lipoprotein synthesis, cholesterol metabolism, and processes involving triglycerides. In addition, the liver plays an important role in the metabolism of fat-soluble vitamins, particularly vitamins A, D, E, and K. Another major function of the liver is detoxification. Numerous chemical substances entering the body through food, medications, or other sources undergo enzymatic metabolism in the liver. The liver also plays an important role in immune defense. Kupffer cells within the liver phagocytose bacteria, cellular debris, and other particles delivered through the portal circulation. In this regard, the liver serves as an important biological barrier against microorganisms that may pass from the gastrointestinal tract into the systemic circulation.

One of the liver's important distinguishing characteristics is its remarkable regenerative capacity. Following surgical removal or injury of a portion of the liver parenchyma, restoration of liver volume and function may occur through proliferation of the remaining hepatocytes and other regenerative mechanisms. This characteristic is one of the principal biological factors that makes living-donor liver transplantation possible. However, the regenerative capacity of the liver is not unlimited. Prolonged chronic inflammation, fibrosis, cirrhosis, or severe necrotic processes can disrupt the normal architecture of the hepatic parenchyma. Consequently, regenerative processes become less effective, and hepatic failure may develop. In patients with end-stage liver disease, liver transplantation is considered when conservative treatment is no longer sufficient to adequately prolong survival.

Chronic viral hepatitis, alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease, autoimmune liver diseases, cholestatic disorders, inherited metabolic syndromes, and hepatic tumors may lead to progressive deterioration of liver function. As the disease progresses, fibrosis increases, resulting in cirrhosis and portal hypertension. During the decompensated stage, patients may develop ascites, variceal bleeding, jaundice, hepatic encephalopathy, and other severe complications. In end-stage liver failure, the liver is unable to adequately perform its metabolic, synthetic, and detoxification functions. Under these circumstances, liver transplantation becomes one of the principal life-saving treatment options.

In modern transplantation practice, either a deceased-donor liver or a portion of a living donor's liver may be transplanted, depending on the type of donor organ. Liver transplantation is a complex, multistep surgical procedure in which anatomical continuity is restored between the hepatic artery, portal vein, hepatic veins, and biliary tract of the donor graft and the corresponding structures of the recipient. Technically precise vascular and biliary anastomoses

are essential for successful graft function. Post-transplant complications can be classified into biliary, vascular, infectious, and immunological categories. Among vascular complications, hepatic artery thrombosis is of particular clinical importance. Thrombosis of the hepatic artery markedly reduces or completely interrupts arterial blood flow to the liver graft. Although portal venous inflow may remain intact, the biliary tract is highly dependent on arterial blood supply and is therefore particularly susceptible to ischemic injury.

Following liver transplantation, hepatic artery thrombosis results in impaired arterial perfusion of the liver graft. This process may cause severe ischemic changes, particularly in the biliary tract. Complications such as biliary necrosis, biliary strictures, bile leaks, hepatic abscesses, and sepsis may develop. In severe cases, graft function may be completely lost, necessitating retransplantation. Hepatic artery thrombosis is considered one of the most common and serious arterial complications following liver transplantation. Advances in microsurgical techniques have also become important in the prevention of HAT. Thus, the anatomy of the liver, its dual blood supply, and the high dependence of the biliary tract on arterial blood flow are fundamental to understanding the clinical significance of hepatic artery thrombosis. These anatomical and physiological characteristics make disruption of arterial blood flow after liver transplantation a potentially life-threatening complication.

Therefore, it is important to examine in greater detail the **etiology, pathogenesis, and risk factors** of HAT. Hepatic artery thrombosis following liver transplantation is a multifactorial pathological process in which surgical, anatomical, hemodynamic, immunological, and hemostatic factors may act in combination. The principal mechanisms underlying thrombosis can be explained by Virchow's triad: vascular endothelial injury, abnormal blood flow, and activation of the coagulation system. During transplantation, an arterial anastomosis is created between the donor and recipient arteries. Because of the technical complexity of this procedure, arterial wall injury, intimal dissection, anastomotic narrowing, or arterial kinking may occur. These alterations can reduce arterial blood flow and create conditions favorable for thrombus formation. In addition, ischemia-reperfusion injury occurring during transplantation may impair endothelial function and exacerbate local inflammatory responses. Endothelial dysfunction promotes platelet activation and activation of the coagulation cascade, thereby increasing the likelihood of thrombus formation.

The anatomical characteristics of the hepatic artery are also of considerable importance. A small donor or recipient arterial diameter, anatomical variations of the hepatic arterial system, size mismatch between the arteries, and the need for additional arterial reconstruction can increase technical complexity. In particular, the small vessel caliber encountered in pediatric transplantation is an important risk factor for HAT. Hepatic artery stenosis also plays an important role in the development of thrombosis. Stenosis at the anastomotic site reduces arterial blood flow and may result in turbulent and sluggish flow in the distal arterial segments. Consequently, favorable hemodynamic conditions for thrombus formation may develop. Therefore, timely detection of post-transplant hepatic artery stenosis is an important component of HAT prevention.

Clinical Manifestations of Hepatic Artery Thrombosis; The clinical presentation of hepatic artery thrombosis following liver transplantation depends on the timing of thrombus development, the degree of arterial occlusion, and the extent of ischemic injury to the graft. Particularly in early HAT, clinical manifestations are often nonspecific and may include rapid

deterioration of the patient's general condition, fever, jaundice, a marked elevation in liver enzyme levels, and signs of sepsis. In some cases, however, HAT may initially be clinically silent and detected only through laboratory testing or Doppler ultrasonography. In early HAT, severe impairment of arterial blood supply to the graft results in ischemic injury to hepatocytes. Consequently, aminotransferase levels, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT), may increase markedly within a short period. In severe cases, hepatic failure, metabolic acidosis, coagulopathy, and hemodynamic instability may develop. In some patients, the clinical presentation may include fulminant hepatic necrosis and sepsis.

Later-onset HAT is more commonly associated with ischemic injury to the biliary tract. Such patients may develop cholestasis, jaundice, bile leaks, biloma, biliary strictures, recurrent cholangitis, hepatic abscesses, and sepsis. Therefore, HAT should be considered in the differential diagnosis when unexplained biliary complications or recurrent infections occur during the post-transplant period.

Risk factors contributing to the development of HAT can be categorized into donor-related, recipient-related, surgical, and postoperative factors. Donor age, anatomical characteristics of the hepatic artery, and vessel quality may influence transplantation outcomes. A small donor arterial diameter or anatomical arterial variants can make arterial anastomosis technically more challenging. Some studies have also demonstrated an association between advanced donor age and the risk of HAT. Prolonged cold ischemia time of the donor organ is another important factor. Prolonged ischemia may exacerbate endothelial injury within the graft and lead to increased oxidative stress and inflammatory responses during reperfusion. These processes may increase the susceptibility to arterial thrombosis. Recipient age, body weight, coagulation status, and previous surgical procedures may also influence the development of HAT. In particular, patients with low body weight and pediatric recipients may have a higher risk of thrombosis because of the small caliber of their arterial vessels. Repeat liver transplantation is another important risk factor for HAT. Previous surgery may result in perivascular adhesions, distortion of normal anatomy, and increased technical difficulty during arterial reconstruction, thereby complicating subsequent transplantation. In some patients, hypercoagulable states may also contribute to thrombus formation. The balance of the coagulation system changes substantially after liver transplantation. Consequently, the risks of both bleeding and thrombosis may coexist in the same patient.

One of the most important risk factors for HAT is the technical characteristics of the arterial anastomosis. Intimal injury during anastomosis, inadequate alignment of the arterial walls, excessive tension on the sutures, or arterial kinking may impair blood flow. Prolonged operative time has also been reported as a factor associated with HAT. Extended surgical procedures may contribute to hemodynamic instability, increased blood loss, and prolonged ischemic exposure of the graft. Complex arterial reconstruction or the use of aortohepatic conduits may also increase the risk of thrombosis. In particular, when unusual arterial anatomical variants are present, the surgical technique must be selected on an individualized basis. Post-transplant infections may also play a role in the pathogenesis of arterial thrombosis. In particular, cytomegalovirus (CMV)-related conditions have been associated with an increased risk of HAT. Previous studies have reported that CMV serostatus mismatch, specifically a seropositive donor and a seronegative recipient, may be associated with an increased risk of early HAT. During acute rejection, inflammation and endothelial injury within

the graft may be intensified. This may further contribute to impaired microcirculation and increase the likelihood of thrombotic processes. Once HAT is diagnosed, the choice of treatment strategy depends on the timing of thrombosis, graft viability, the patient's overall clinical condition, the anatomical location of the thrombus, and the resources and expertise available at the transplant center.

Early Diagnosis of Hepatic Artery Thrombosis; Early diagnosis of hepatic artery thrombosis (HAT) is crucial for increasing the likelihood of graft salvage. Therefore, in the post-transplant period, routine Doppler ultrasound surveillance, rather than waiting for clinical signs to develop, is an important diagnostic strategy. Doppler ultrasonography is a non-invasive, rapid, and bedside imaging modality and is considered the first-line examination for assessing hepatic arterial blood flow.

Color Doppler and spectral Doppler examinations are used to evaluate the hepatic artery at the anastomotic site, the main hepatic arterial trunk, and the intrahepatic arterial branches. The most important Doppler finding suggestive of HAT is absence of detectable blood flow in the hepatic artery. In the pre-thrombotic stage, decreased or absent diastolic flow, an increased resistive index, reduced systolic flow velocity or amplitude, and changes in the arterial waveform may be observed. Subsequently, complete loss of arterial flow raises a strong suspicion of hepatic artery thrombosis. Physiological hemodynamic changes during the early postoperative period should also be taken into consideration when interpreting Doppler findings. For example, during the first days after transplantation, the resistive index may be transiently elevated because of graft edema and arterial vasospasm. Therefore, assessment should not rely on a single Doppler parameter; rather, the dynamic changes in arterial blood flow and the results of serial examinations should be taken into account.

If hepatic arterial flow is not detected on Doppler ultrasonography or the findings are inconclusive, computed tomography angiography (CTA) or digital subtraction angiography (DSA) may be performed to further assess hepatic arterial patency. CTA can help determine the location of arterial occlusion, identify ischemic changes within the graft parenchyma, and evaluate other vascular complications. DSA provides detailed visualization of the arterial anatomy and, in selected cases, allows diagnosis and endovascular treatment to be performed during the same procedure.

Thus, early diagnosis of HAT is based on a sequence of clinical surveillance → laboratory monitoring → Doppler ultrasonography → CTA or DSA when indicated. If Doppler examination demonstrates loss of hepatic arterial flow or findings strongly suggestive of thrombosis, further diagnostic evaluation and revascularization should not be delayed. Early detection and prompt restoration of hepatic arterial blood flow increase the likelihood of graft salvage.

In early HAT, the primary objective is to restore arterial blood flow to the graft as rapidly as possible. Treatment options include surgical revascularization, thrombectomy, and revision of the arterial anastomosis. Surgical thrombectomy allows direct removal of the thrombus and restoration of arterial blood flow. If a technical problem is identified at the anastomotic site, surgical revision or reconstruction of the anastomosis may be required. In early HAT, thrombectomy followed by revision of the arterial anastomosis is considered a primary treatment approach in selected cases. Endovascular treatment is increasingly used in modern liver transplantation. Available techniques include catheter-directed thrombolysis, mechanical thrombectomy, balloon angioplasty, and stent placement.

During catheter-directed thrombolysis, a thrombolytic agent is delivered directly into the artery at the site of the thrombus. Compared with systemic thrombolysis, this approach allows local delivery of the drug at a higher concentration and may, in selected cases, reduce systemic exposure and the risk of bleeding. Mechanical thrombectomy is aimed at physically removing the thrombus. Using modern endovascular devices, the thrombus can be aspirated or extracted with specialized thrombectomy systems. However, these procedures should be performed in centers with experienced interventional radiologists and multidisciplinary liver transplantation teams.

If HAT is secondary to hepatic artery stenosis, the arterial lumen may be enlarged by balloon angioplasty or stent placement. Endovascular treatment is particularly important in selected patients with later-detected arterial complications. If revascularization is unsuccessful or irreversible ischemic injury to the graft has developed, liver retransplantation may be required. Retransplantation remains a complex clinical challenge because of donor organ shortages and the often critical condition of affected patients.

Thrombosis prophylaxis after liver transplantation is a complex clinical issue because these patients are simultaneously at risk of both thrombosis and bleeding. Therefore, the use of anticoagulant or antiplatelet therapy should be assessed on an individual basis. In patients at high risk of HAT, the prophylactic strategy should take into account donor and recipient characteristics, the type of arterial reconstruction, coagulation status, and the postoperative hemodynamic condition.

One of the most important strategies for reducing the incidence of HAT is the creation of a technically sound arterial anastomosis during transplantation. Avoiding injury to the arterial wall, ensuring appropriate vessel alignment, and confirming adequate arterial blood flow at the end of the procedure are essential. During the postoperative period, regular Doppler ultrasound surveillance is an important component of preventive and diagnostic management. Early detection of reduced or absent arterial blood flow may allow HAT to be identified before clinical symptoms develop. Timely detection and treatment of hepatic artery stenosis are also important in preventing HAT, as a significant untreated stenosis may subsequently progress to arterial thrombosis.

Conclusion; The liver is a complex organ that performs numerous vital functions, including metabolism, protein synthesis, detoxification, immune defense, and bile production. Its unique dual blood supply is essential for normal physiological function. In particular, the high dependence of the biliary tree on arterial blood flow makes the hepatic artery a critical vessel after liver transplantation.

Although liver transplantation is an effective life-saving treatment for patients with end-stage liver disease, postoperative vascular complications can pose a serious threat to graft function. Hepatic artery thrombosis is one of the most severe of these complications and, particularly when it develops early after transplantation, may result in graft loss and patient mortality.

The development of HAT is associated with multiple factors, including technical characteristics of the arterial anastomosis, small-caliber vessels, arterial anatomical variants, retransplantation, prolonged operative time, ischemia–reperfusion injury, hypercoagulable states, and other contributing factors. At present, the key principle in the management of HAT is early detection followed by prompt revascularization. Doppler ultrasound surveillance plays

a central role in initial detection, whereas CTA and DSA are important for confirming the diagnosis and guiding treatment.

Modern endovascular techniques—including catheter-directed thrombolysis, mechanical thrombectomy, angioplasty, and stent placement—are increasingly being used in selected patients as alternatives or adjuncts to surgical treatment. Nevertheless, surgical revascularization and, when necessary, retransplantation remain important treatment options for early HAT.

Overall, reducing the incidence and consequences of HAT after liver transplantation requires optimization of surgical techniques, identification of high-risk patients, regular postoperative Doppler ultrasound surveillance, and timely use of interventional radiology. Early diagnosis and an individualized treatment strategy are key factors in improving graft salvage and long-term patient outcomes

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