Editorial

The significance of severe postoperative complications on liver regeneration

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The liver is an extraordinary organ known for its remarkable regenerative capacity (1). This regenerative ability lays the foundation for various therapeutic approaches, such as partial hepatectomy (PHx), split-liver transplantation, live-donor liver transplantation, and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS). However, insufficient liver regeneration or impaired functional recovery poses a significant risk for posthepatectomy liver failure (PHLF). PHLF has been identified as the leading cause of mortality within 90 days after surgery, and currently, there is no specific medication or combination of drugs available to treat patients with PHLF (2,3). Therefore, accurate preoperative prediction and early identification of PHLF are crucial in clinical practice.

Recently, Rassam *et al.* conducted a study to assess the early postoperative changes in remnant liver function, volume, and liver stiffness after major liver resection using perioperative technetium-99m mebrofenin hepatobiliary scintigraphy (HBS), computed tomography (CT)-volumetry, and transient elastography (TE) (4). The study included 18 patients who underwent major liver resection, with 10 of them (56%) experiencing severe complications, and one patient (6%) developing liver failure. The results demonstrated that overall, both the function and volume of the remnant liver significantly increased by the 5th postoperative day. However, while the remnant liver volume continued to increase after 4–6 weeks, there was no significant further increase observed in liver function. This suggests that the recovery of liver function is faster than the recovery of liver volume following major liver resection. Given that more than half of the patients experienced severe postoperative complications, the authors further analyzed the recovery trajectory of liver function and volume based on whether patients were accompanied by these complications. It was found that severe postoperative complications notably hindered the recovery of both liver function and volume. Specifically, liver function did not show a significant increase on the 5th postoperative day, which is strongly associated with the development of PHLF. Regarding liver stiffness, the elasticity of the future remnant liver (FRL) significantly increased during the first 5 postoperative days and gradually recovered after 4–6 weeks. However, for patients with severe postoperative complications, there was a tendency towards a larger increase in liver elasticity 5 days after resection, and it did not exhibit a clear decrease after 4–6 weeks. This elevation in liver stiffness is linked to various factors associated with PHLF, including hemodynamic changes, inflammation, acute cellular rejection, and parenchymal edema (5). Based on these findings, the study suggests that HBS and TE are promising non-invasive tools for evaluating patients at risk of PHLF.

There are various parameters associated with PHLF, which can be categorized into patient-, liver-, or surgery-related factors. Patient-related factors include sex, age, sepsis, metabolic conditions, inadequate renal function, and cardiopulmonary diseases. Liver-related factors encompass

steatosis, fibrosis grade, cholestasis, portal hypertension, and prior exposure to neoadjuvant chemotherapy. Surgery-related factors mainly consist of the FRL size, blood loss, transfusion requirements, vascular occlusion techniques, and operative time (3,6). In addition to the well-documented risk factors mentioned above, severe postoperative complications, as highlighted by Rassam *et al.*, also have detrimental effects on liver regeneration and functional recovery (4). Postoperative sepsis may arise from multiple sites and multifactorial issues, including infected hematomas and biliary collections. Bacterial endotoxins interact with Kupffer cells and hepatocytes, inhibiting the production of cytokines crucial for early-phase liver regeneration (7). Sepsis further exacerbates PHLF and is a common cause of death in patients with established PHLF (8). Jaundice significantly increases the risk of morbidity after surgery (9), but bile leakage can result in the loss of bile salts, affecting the activity of fibroblast growth factor 19, which in turn hampers postoperative liver regeneration (10,11). Following partial liver resection, increased flow and pressure in the portal vein exert shear stress on sinusoidal endothelial cells, triggering the release of oxide and promoting liver regeneration (12). Therefore, partial ischemia not only reduces the actual volume of the FRL but also weakens its regenerative capacity. Postoperative ascites can stem from multiple causes, such as insufficient renal function, impaired synthesis capacity of the FRL, and portal vein hypertension. Excessive portal venous flow, typically exceeding 20 mmHg, leads to increased sinusoidal pressure, endothelial damage, and sinusoidal hemorrhage (13). Therefore, it is crucial to strike a balance in increasing portal venous flow to stimulate liver regeneration without reaching the threshold of hepatocyte injury.

In summary, preventing and effectively managing PHLF is crucial in hepatectomy-based surgeries. Adequate treatment of postoperative complications and early identification of PHLF using optimal non-invasive methods are essential for improving outcomes in patients undergoing major liver resection. Additionally, the use of the 70% PHx model in rodents can provide valuable insights into the physiological processes and help identify potential therapeutic targets in liver regeneration (14).

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