



## Editorial

# Prediction and Prevention of Post-hepatectomy Liver Failure: Where Do We Stand?

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No standardized description or definition of post-hepatectomy liver failure has been introduced. Definitions based on the degree of rise in serum total bilirubin or prolongation of prothrombin time postoperatively were predictive of short-term mortality. Due to lack of universal definition, however, its prevalence is variable but may reach up to 12% post-hepatectomy, according to the definition by International Study Group of Liver Surgery, and or 34%, as in some reports.<sup>1</sup>

The normal liver starts to regenerate within 2 weeks, and is completed mostly after 3 months; the process is initiated by increased production of endothelial nitric oxide in liver sinusoids, secondary to the shear stress on vascular endothelium caused by sudden increase in portal flow after partial hepatectomy and augmented by increased expression of transcription factors, such as c-fos and c-myc.<sup>2</sup> The therapeutic behavior after partial hepatectomy should be directed towards protection of residual hepatocyte function and microvascular functional organization, rather than restoration of liver volume.

Post-hepatectomy liver failure can be defined as post-operative failed ability of the liver to maintain the synthetic, excretory and detoxifying functions with coagulopathy and hyperbilirubinemia on the 5th post-operative day, in addition to the development of clinical symptoms, such as encephalopathy and ascites, in combination with results from liver function tests. Balzan *et al.*<sup>3</sup> established a definition using 50-50 criteria, by which PT <50% and serum bilirubin >50 µmol/L on the 5th day of surgery was associated with >50% risk of early post-operative mortality. Another study found that a peak serum bilirubin concentration of >7 mg/dL strongly predicted liver-related death and worse postoperative outcomes after hepatectomy.<sup>4</sup> Schindl *et al.*<sup>5</sup> provided a classification for the severity of post-hepatectomy liver failure into four grades and included four parameters (i.e. total serum bilirubin concentration, prothrombin time, serum lactate concentration, and grade of encephalopathy).

The International Study Group of Liver Surgery had postulated a definition of post-hepatectomy liver failure<sup>6</sup> in which a postoperatively acquired deterioration in the ability

of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased international normalized ratio (or need of clotting factors to maintain normal international normalized ratio) and hyperbilirubinemia on or after the fifth postoperative day. Other obvious causes for the biliary obstruction should be excluded. As such, Grade A represents abnormal laboratory parameters requiring no change in the clinical management of the patient, Grade B results in a clinical management but without invasive treatment, and Grade C results in a clinical management requiring invasive treatment.

A risk score was developed to define post-hepatectomy liver failure after evaluation of 1,269 patients, and was able to identify the extent of surgery and pre-operative bilirubin, international normalized ratio, and creatinine as predictors of post-hepatectomy liver failure.<sup>7</sup> Risk factors of liability to post-hepatectomy liver failure are patient related as increasing age above 65 years; however, other studies found no actual relation of age with operative outcomes, the presence of malnutrition was associated with higher incidence of post-hepatectomy liver failure and that higher body mass index was associated with higher risk of hepatic dysfunction. Furthermore, sepsis and associated endotoxemia was found to impair the ability of Kupffer cells to produce and transfer regenerative cytokines. Renal and cardiopulmonary impairment and preoperative thrombocytopenia have also been linked to high risk of post-hepatectomy liver failure, as platelet-derived serotonin is important for hepatic regeneration and tissue repair after hepatectomy and any medications that reduce intraplatelet serotonin should be avoided.<sup>8</sup> Liver-related risk factors, such as fatty liver disease, have been associated with inflammation, due to higher risk of ischemia-reperfusion injury in the steatotic liver, severity of cirrhosis with the presence of ascites, hyperbilirubinemia and the harmful effects of preoperative chemotherapy of colorectal cancer on the occurrence of post-hepatectomy liver failure as irinotecan and oxaliplatin-based chemotherapies which induce fatty infiltration, sinusoidal dilation and biliary complications.

Additional operation-related risk factors are intraoperative blood loss of more than 1,000–1,200 mL, which may stimulate bacterial translocation, systemic inflammatory response and coagulopathy, and technical-related factors including vascular resections or repair, or injury to tissues around the portal triad and hepatoduodenal ligament. The future liver remnant volume/standardized liver volume ratio should exceed 20%. In line with this, the body weight ratio of liver volume cutoff value of 0.5 is highly predictive of post-hepatectomy liver failure.

A major hepatic resection is defined as resection of three or more segments. The remnant liver volume is an impor-

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tant parameter, and another is the small-for-size syndrome, if the graft recipient weight ratio is less than 0.8–1.0 or less than half of standard/estimated liver volumes.<sup>9</sup>

Reduced functional liver volume increases the portal pressure suddenly, with an increase in the intra-sinusoidal pressures and endothelial shear stress. Patients with a small future liver remnant are at a higher risk for post-operative failure. The future liver remnant is calculated as the ratio of the remnant liver volume and the total functioning liver volume, with the latter being calculated by subtracting the tumor volume from the total liver. At least, the future liver remnant should be 20% of normal livers and 40% of cirrhotic liver.

Assessment of patients can be achieved qualitatively by Child-Turcotte-Pugh scoring. Patients with Child's B or C are not candidates for liver resection, an additional scoring system, the model for end stage liver disease is useful, with a score >10 having a higher mortality risk ( $p < 0.001$ ). Metabolic excretion tests, such as ondocyanine green retention rate, are also used and a cut-off value of 14% can triage patients liable for significant morbidity. Other metabolic tests, mainly the LiMax breathe test (methacetin injection), can predict postoperative liver function.

Prevention of post-hepatectomy liver failure can be achieved by modulating the porto-splenic circulation and thereby impacting the remnant liver volume. The portal vein can be embolized to stimulate the production of nitric oxide in patients with cirrhosis and expected future liver remnant of <40. The sluggish portal flow after embolization will enhance arterial flow in the embolized segments (i.e. hepatic arterial buffer response). Hepatic venous outflow reconstruction can ensure an adequate venous outflow; minimizing the venous kinks and congestion (on the surgical table) is essential for preventing post-hepatectomy liver failure.

In situ hypothermic liver perfusion decreases the cellular activity via hypothermia and minimizes ischemia-reperfusion injury. Splenectomy may be a feasible procedure, as the spleen shares 25–30% of the portal flow, reaching nearly 50% in cases of splenomegaly, due to portal hypertension; thus, splenectomy lessens the stress on endothelial lining and hepatocytes with an increase in hepatic arterial buffer response.

In the current research by Xu *et al.*<sup>10</sup> a total of 492 patients who had undergone hepatectomy from July 2015 to June 2018 were retrospectively analyzed. Multivariate analysis identified three preoperative variables, including total bilirubin ( $p = 0.001$ ), international normalized ratio ( $p < 0.001$ ) and platelet count ( $p = 0.004$ ), and two intra-operative variables, including extent of resection ( $p = 0.002$ ) and blood loss ( $p = 0.004$ ) as independent predictors of post-hepatectomy liver failure. The area under the receiver operating characteristic curve of the postulated score was 0.838, with an advantage over the model for end-stage liver disease score and albumin-bilirubin and platelet-albumin-bilirubin scores (0.723, 0.695 and 0.663, respectively;  $p < 0.001$ ). That report also provided a new nomogram to predict post-hepatectomy liver failure, composed of peri-

operative factors, but other intra-operative variables may affect the outcome, such as the extent of resection and the amount of blood loss. The score was easy to calculate based on readily available pre-operative and intra-operative data and helps to identify patients at higher risk.

That study had involved patients either with benign or malignant lesions, so that tumor number, size and associated biomarkers were not analyzed; yet, inadequate future liver remnant volume can lead to post-hepatectomy liver failure. Measuring future liver remnant volume and function should have been studied; however, utilizing simple and readily available variables may significantly contribute to the postoperative work-up of these patients for better outcome.

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## Conflict of interest

The author has no conflict of interests related to this publication.

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