Editorial

Liver resection, and technical advances to mitigate post-hepatectomy liver failure

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The liver is the chemical factory in human body and a unique organ in five ways: (I) it is the largest internal human viscera; (II) anatomically it is unique due to the duality of blood and oxygen supply; (III) among all abdominal viscera, liver receives the highest amount of blood supply in resting state; (IV) physiologically liver is unique as pathology management decisions are not only determined by pathology but also by inherent liver function; and (V) clinically it is unique as it is the commonest site of metastatic disease from solid organ primaries. These unique characteristics increase the challenges in managing liver conditions, especially liver resection. In addition to general operative risks, and liver-specific operative risks; one unique risk of liver resection is an insufficient future liver remnant (FLR) resulting in post-hepatectomy liver failure (PHLF); as unlike renal dialysis, liver dialysis is not a practical standard of care. PHLF risk is highest in hepatocellular carcinoma (HCC) patients with cirrhosis and estimated between 8% and 12% in patients undergoing major liver resection, with a risk of mortality (1). Thus, prevention of PHLF is an essential pillar of safe liver surgery. It is a duty of liver surgical teams to audit and report the clinical outcomes to disseminate not only novel techniques, but also routine good clinical care components for dissemination and adoption by wider surgical community. The multicenter prospective study by Liang *et al.* serves both this purpose (2).

The authors report a case series of 327 patients from five Chinese hospitals with a constructed and validated combined pre-and intra-operative nomogram that predicts PHLF risk. Six variables included were hepatitis B virus (HBV) DNA level, indocyanine green retention at 15 minutes (ICG-R15), total bilirubin, prothrombin time, pre-operative cirrhotic severity scoring (CSS), and intra-operative direct liver stiffness model (DSM). While the first four are familiar to most physicians, the last two deserve mention. CSS is dissimilar to the Child-Pugh (CP) score and includes four variables: severity of esophageal varices, portal vein diameter, spleen thickness, and platelet count (3). DSM is a novel invasive method that involves a direct probe placement over the liver during open surgery and is dissimilar to non-invasive transient elastography scan. The authors reported better PHLF prediction accuracy of a combined pre-and intra-operative nomogram than pre-operative alone [area under the curve (AUC): 94.4% *vs.* 93.1%]. The core results of this study are not unexpected and I shall discuss four observations that this study brings to light.

Firstly, patient selection is an integral component of safe liver surgery. With advances in critical care, innovative technologies, and surgical skill-set refinement, the selection

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of patients eligible for liver resection is expanding. While enhanced recovery after surgery (ERAS) initiatives are good care, elderly frail patients benefit most from prehabilitation initiatives and a "non-rushed" care delivery (4). Auditing one's practice is a good policy, as good science cannot exist without good data. The existing clinical practice guidelines cannot replace the care plans that must be customized to local infrastructure and an individual patient (5). I commend the authors for sharing their observation of higher PHLF risk in patients with ICG-R15 of 15% *vs.* 10%. This likely explains an excellent 90-day mortality statistic that merges with 30-day mortality. Currently, at Tan Tock Seng Hospital (Singapore), we use ICG-R15 of 15% for major hepatectomy case selection and our 90-day mortality risk (3.7%) is higher than 30-day mortality risk (2.4%); both being much higher than authors' report (6). Of course, a head-to-head comparison is unfair as differences in patient co-morbidity, patient selection, and study time points introduce bias. For example, Liang *et al.* excluded patients with multinodularity and macrovascular invasion. However, the results of Liang *et al.* should stimulate the international community to reconsider tweaking the threshold of ICG-R15 statistic to 10% instead of the traditional 15%. Note, despite such stringent case selection, and assuming good care provision, some patients died. This suggests that PHLF and mortality risk can be minimized, but not eliminated.

The second consideration is size-based case selection or risk prediction. In general tumor size is a determinant of staging, prognosis, and clinical outcomes of the vast majority of solid organ malignancies. For various reasons, many existing HCC staging systems exclude size-based staging despite the knowledge that size increases the risk of vascular invasion, distorts structural anatomy with technical difficulty in resection, and sheer common wisdom that the larger the number of cancer cells, the higher is the likelihood of random mutations and immune escape with poor tumor differentiation that determines survival outcomes. I have used simple mathematical formula and, assuming a spherical shape of HCC, computed that a 10 cm HCC has 8 times the volume of a 5 cm HCC and a 15 cm HCC has about 3 times the volume of 10 cm HCC (7). In a local audit of 18 patients with super-giant HCC (defined as size ≥15 cm), 12 patients (66.7%) had microvascular invasion, 9 patients (50%) had poor tumor differentiation, 3 patients (16.7%) had macrovascular invasion, and 1 patient sustained 90-day mortality (7). To disregard the size for staging and prognostication is an error and a matter ripe for an urgent review. The challenge is defining an ideal cut-off size, but disregarding size entirely is not a perfect solution to the dilemma of optimal cut-off. All three deaths in the study by Liang *et al.* are recorded in patients with 9 cm and larger HCC. In patients with large HCC, a possibility exists that the remnant liver surface area may be small for the DSM probe to take readings from different parts, thus affecting the accuracy of liver stiffness results. However, this needs to be tested and validated or refused by appropriate studies. As DSM probe technology is not refined to accommodate laparoscopic measurement, at least for the time being, the eligible patient pool for any clinical study is limited to patients undergoing open liver resection.

The third consideration is the timing of PHLF prediction, especially if surgery could be avoided or perioperative care modified in patients with predicted high PHLF risk. Ideally, the prediction should exclude post-operative variables, as the best management of PHLF is its prevention, and surgery is a non-reversible situation. Thus, I commend the authors for limiting the selection of variables to pre- and intra-operative factors. Pre-operative factors alone are "the best" as surgery may not be offered if PHLF risk is considered high. Non-surgical modalities like a combination of local ablation along with trans-arterial chemoembolization (TACE) (8), and radioembolization (9) might be provided to induce ischemic preconditioning, downstaging, or as a definitive therapy. Thus, the findings of this study are attractive as the nomogram based on pre-operative variables is at least non-inferior compared to both pre-and intra-operative variables. In addition, if a patient is deemed to be at high PHLF risk and liver resection is judged to be the optimal therapy by multidisciplinary teams, additional considerations like avoidance of the Pringle maneuver, perioperative administration of steroids (10), parenchyma sparing resections (11), pre-operative portal vein embolization, and associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) (12) might be considered. While these modalities are attractive, they also do not eliminate PHLF risk. For example, a local audit of 10 ALPPS patients revealed that volumetric increase does not correspond to liver function enhancement and one patient developed PHLF (13).

Lastly, at least two peripheral considerations from this study deserve mention. The first consideration is the Barcelona Clinic for Liver Cancer (BCLC) criteria and its application in HCC management. At least in the Asian context, if not global, it is evident liver resection criteria are more liberal than BCLC recommendations. In terms

of the Milan (criteria for liver transplantation) analogy, this can be summed as "everybody knows about it, somebody speaks about it, and nobody follows it strictly". This does not undermine the criteria itself, as BCLC is a reference standard against which other systems are compared (14), but it does caution physicians to offer other therapeutic choices to their patients accounting for geographic differences and personal experiences. Though the authors have not mentioned BCLC in the study, and excluded patients with multinodularity and macrovascular invasion, the case selection is more likely to be liberal than the traditional BCLC criteria. The second consideration relates to the patient's perspective. For understandable reasons, most surgical and technical reports are short-sighted with limited follow-up. Thus, though the 90-day mortality risk is low, a patient's interest is beyond this timeframe. Our unit has reported that 1-year mortality risk is higher than a 90-day mortality risk and can be predicted by pre-operative variables like CP score, multinodularity, and macrovascular invasion (15). As the authors excluded patients with multinodularity and macrovascular invasion, the 1-year mortality risk may also be low. It is my personal opinion that, in prospective studies, surgeons should report not only 90-day outcomes but also 1-year outcomes as there are surgical complications (e.g., bile leak) that drag clinical care beyond 90 days and also impact adjuvant therapy initiation and choice, with an impact on survival and quality of life. Though adjuvant therapy is not a routine standard of care for all HCC patients, there is emerging evidence that in patients with high recurrence risk, it might confer benefits.

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Footnote

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