Editorial

A novel comprehensive ALPPS preoperative risk assessment (CAPRA) score is beneficial in creating a treatment strategy for advanced liver malignancy

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Curability and safety are essential for patients with advanced liver malignancy undergoing extended liver resection. If the future liver remnant (FLR) volume is insufficient, portal embolization with or without hepatic arterial or venous embolization or a conventional two-stage hepatectomy (TSH) can be performed (1,2). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced in 2007. It is used in patients with extremely small FLR. Initially, ALPPS was an innovative high-risk procedure with high mortality, ranging from 9% to 17% (3-5). Several studies identified the risk factors for mortality after ALPPS, and developed mortality prediction scoring to improve patient selection (6-10). Introducing these scores resulted in a dramatic decrease in early mortality to <5%. A recent systematic review by updated traditional and network meta-analyses found no difference in mortality between ALPPS, TSH, and one-staged hepatectomy following portal vein embolization/ligation (11). A randomized controlled trial, LIGRO, showed that ALPPS for patients with colorectal liver metastases (CRLM) improved survival compared with TSH and did not increase morbidity and morbidity (12). ALPPS can provide rapid liver regeneration; however, its oncological advantages and disadvantages have not been fully understood (10). The number of ALPPS being performed is increasing. According to the ALPPS registry (https://www.alpps.net/), by 2020, over 1,200 ALPPS procedures had been performed worldwide. The main indications for ALPPS were CRLM (64%), hepatocellular carcinoma (14%), and intrahepatic and extrahepatic cholangiocarcinoma (12%).

Dr. Ivan Capobianco and his colleagues created a novel comprehensive ALPPS preoperative risk assessment (CAPRA) score which showed excellent validation results in a recently published *HepatoBiliary Surg Nutr* 2022 (13). In all, 451 patients undergoing ALPPS from 13 high-volume centers worldwide were enrolled. The primary endpoint of the study was postoperative mortality, defined as procedure-related mortality after ALPPS Stage 1 or 90-day mortality after ALPP Stage 2. Overall mortality was 14.4% (2.2% after Stage 1 and 12.2% within 90 days of Stage 2). Mortality was 9.1% for secondary tumors (CRLM mortality: 9.4%) and 24.5% for primary tumors (cholangiocarcinoma mortality: 27.5% and hepatocellular carcinoma mortality: 19.4%). The predictive ability of the CAPRA was 0.837, which was superior to previous traditional scores; 0.443 for Charlson Comorbidity Index

(CCI), 0.519 for age-adjusted CCI, 0.693 for ALPPS-risk score 1 and 0.807 for ALPPS-risk score 2. After adequate cycles of 1,000 bootstrapping, the C statistic was high enough at 0.793. Finally, the accuracy plot clarified that the optimal postoperative mortality rate was 4.70. In particular, the CAPRA score showed good predictivity even when used during the learning curve. However, there is concern that this study included only patients who completed both steps of the ALPPS, which could affect the results. Previous studies included patients who did not achieve ALPPS stage 2 (6). Although CAPRA was very effective as a total risk score, there was a clear difference in mortality between secondary and primary tumors (9.1% *vs.* 24.5%). Therefore, separate risk scores will be required, at least for secondary and primary tumors.

The reasons for mortality, though important, are not given in this paper. Preoperative comorbidities can cause comorbidity-related death (myocardial infarction, renal failure, thrombosis, and others). As the authors mentioned, comorbidities can reduce the possibility of overcoming postoperative complications once they have occurred. Liver failure is the most common cause of mortality after ALPPS (3). In this study, the degree of liver disease was evaluated with CCI or aCCI. These depend on the presence of cirrhosis, portal hypertension, and a history of variceal bleeding. In patients contemplating ALPPS, such advanced liver disease was rarely observed. The safety of liver resection, including ALPPS, has been assessed based on the liver functional reserve and FLR. FLR is investigated by three-dimensional reconstruction with CT volumetry. The correct functional FLR can be estimated with 99mTc-galactosyl human serum albumin scintigraphy or 99mTc-mebrofenin hepatobiliary scintigraphy single-photon emission computed tomography/CT fused images (1). However, such functional volumetry can overestimate the remnant liver function in ALPPS (10). Therefore, we suggest the authors reevaluate the value as a risk factor of comorbidities in combination with liver function and volume parameters.

It is commendable that the CAPRA score for the total risk of ALPPS is constructed based on parameters that can be evaluated before ALPPS Stage 1, unlike the previous ALPPS-risk scores (6,8). The parameters consist of patient characteristics, including tumor type, comorbidities, and the type of ALPPS procedure. The CAPRA score is calculated using the following formula: (0.1 × age) – (2 × body surface area [BSA]) + 1 (for primary liver tumor) + 1 (for severe cardiovascular disease) + 2 (for moderate or severe DM) + 2 (for renal disease) + 2 (for classic ALPPS). What can we do to decrease the risk of postoperative mortality? BSA is negatively related to the CAPRA score. Preoperative immune modulating nutrient support for poorly nourished patients might be helpful to gain body weight and improve sarcopenia (14). In addition, preoperative rehabilitation can modulate the degree of cardiovascular disease and diabetes mellitus. Selecting classic ALPPS adds 2 points to the CAPRA score; 59% of patients underwent classic ALPPS, while 41% underwent some form of technical modification in Stage 1. A partial parenchymal transection (partial ALPPS) has shown overall safety superiority over the classic ALPPS; however, liver regeneration can differ based on the type of ALPPS procedure (10). Modifications of the classic ALPPS have led to annual improvements in mortality (7). The time trend of induction of ALPPS procedures can influence the higher risk of classic ALPPS. The indications for less invasive techniques (laparoscopic ALPPS, portal vein embolization ALPPS, tourniquet ALPPS, and radiofrequency-assisted ALPPS) have limited indications and surgeons are still on the learning curve.

The results of this study are not applicable to all hospitals. The patients were recruited from 13 high-volume hepatobiliary centers, defined as centers with an experience of at least 20 ALPPS each. For CRLM, a total center volume of <20 is one of the risk factors for mortality (8). A high-volume center is not clearly described for overall ALPPS; in contrast, that is defined as an experience of 100 or more liver resections per year for hepatocellular carcinoma (15). In the high-volume centers, the complication rates were comparable to those of the low to intermediate-volume centers because of extended indications for advanced cases. However, a significantly lower incidence of failure to rescue rates can result in lower mortality rates. Failure to rescue rates is defined as the probability of postoperative death among patients with a major complication. This viewpoint one should define a high-volume center for ALPPS from this viewpoint. ALPPS might be recommended to be performed only in the high-volume center. Complications and liver dysfunction after ALPPS Stages 1 and 2 can significantly increase overall ALPPS mortality (6); therefore, safe and sophisticated operative techniques and improvement of failure to rescue rates are essential for each Stage 1 and 2 procedures.

In conclusion, we strongly recommend that the indications for ALPPS should be decided using the CAPRA score in combination with an assessment of liver function and FLR before ALPPS Stage 1. Preoperative

modulation of comorbidity can be helpful. It's beneficial to avoid classical ALPPS if possible. Furthermore, the patients should be re-evaluated before ALPPS Stage 2 using ALPPS-risk score 2 (6).

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