Editorial Commentary

Graft-to-recipient weight ratio: a timeless standard still shaping outcomes

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Liver transplantation (LT) is the optimal treatment for end-stage liver disease. A significant shortage of deceased donors, especially in Asian and Middle Eastern countries has necessitated the development of living donor LT (LDLT). One of the challenges of LDLT in the early postoperative period is small-for-size syndrome (SFSS) caused by a small graft size. SFSS is characterized by portal hyperperfusion leading to persistent cholestasis, coagulopathy, and ascites, and is known to be associated with inferior graft survival after LDLT (1). Traditionally, a graft-to-recipient weight ratio (GRWR) of less than 0.8 has been utilized as a threshold for SFSS, but this threshold has been reduced to a GRWR of 0.6 or 0.7 to maximize donor safety as well as to deal with the ongoing donor shortage (2).

In a recent issue of *Annals of Surgery*, Eguchi and colleagues analyzed a nationwide Japanese cohort of 10,000 LDLTs conducted over 30 years (3). Their analysis found that a GRWR of ≥5 in pediatric cases and <0.6 in adult cases were associated with worse patient survival (PS) after LDLT. Interestingly, they revealed that the threshold of GRWR associated with worse PS in adult LDLT varies according to donor age. Specifically, when the donor age was between 50 and 60 years, patients transplanted with livers having a GRWR of <0.7 exhibited significantly inferior PS. This observation was consistent with a previous single-center report (4). The authors speculated that a reduced number of Kupffer cells or natural killer cells, as well as latent fibrosis seen in grafts from older donors, restrict liver regeneration capacity, making these grafts susceptible to SFSS.

Interaction between donor age and GRWR regarding their impact on survival outcomes is quite reasonable, given that both are risk factors for vascular complications after LT. Donor age is a well-known risk factor for hepatic artery thrombosis (5), and portal hyperperfusion in small-for-size grafts can cause ischemic hepatic artery injury through the hepatic artery buffer response (6). Previously, the Model for End-Stage Liver Disease (MELD) score, venous outflow modulation, and portal inflow modulation have been proposed as potential modulators of functional graft size (7). Fujiki *et al.* showed that venous outflow augmentation can facilitate the use of small left lobe grafts (2). Building upon these studies, the present study from the Japanese Liver Transplantation Society registry introduces new perspectives on optimizing graft volume in LDLT.

Historically, lessons learned from LDLT in Asia have been applied to LDLT and deceased donor LT (DDLT) in the United States. LDLT has played a key role in mitigating waitlist mortalities among women and candidates with small body habitus who have experienced poor waitlist outcomes in the United States due to size mismatch and the incorporation of creatinine in the MELD score (8). Additionally, LDLT has demonstrated a survival benefit for

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patients with lower MELD scores compared to deceased donor LT (9) and is increasingly utilized in transplant oncology. For example, LDLT is employed for unresectable colorectal liver metastasis, allowing LT to be performed appropriately within the overall oncological treatment timeline. Moreover, in the DDLT, surgical techniques developed in LDLT have been adapted for split grafts, an important source of smaller grafts for candidates with small body sizes in the United States (10). Furthermore, the concept of donor-recipient size mismatch applies to deceased donor grafts. Deceased donor grafts do not perform well if they are too small (11), although the extent of size mismatch differs significantly between LDLT and DDLT. This might be because DDLT includes older donors, and grafts are damaged by longer cold ischemia time than living donor grafts, limiting their functional graft volume.

What will be the next step for GRWR in LDLT? Thanks to the tremendous efforts of transplant surgeons over the past three decades, the threshold of GRWR to prevent SFSS appears to have been established. However, as the study by Eguchi *et al.* clearly shows, there is considerable nuance in the relationship between GRWR and clinical outcomes. Not all grafts from living donors are functionally equivalent. Considering the concept of "functional graft volume", measuring liver volume and body weight may not be sufficient. We need to assess this nuance more objectively for living donors and recipients.

For donor assessment, approaches using peripheral blood samples, imaging modalities including nuclear medicine, or molecules already utilized in liver surgery might be applied. For example, non-invasive scoring systems such as the fibrosis-4 index, the steatosis-associated fibrosis estimator (SAFE) score, or the albumin-bilirubin (ALBI) score were initially developed as risk assessment tools for cirrhotic patients. However, the fibrosis-4 index is also known to be useful for risk stratification in healthy individuals. Incorporating such continuous scores for graft assessment might be beneficial in determining the threshold of GRWR. Moreover, in patients undergoing liver resection, imaging modalities such as technetium-99 galactosyl serum albumin (99Tc-GSA) scintigraphy, 99Tc-mebrofenin scintigraphy, or elastography are known to be useful in assessing the risk of postoperative liver failure (12). These modalities might also be useful in stratifying the quality of grafts from living donors. Furthermore, in DDLT, the motive to utilize donation after circulatory death (DCD) donors has necessitated the advancement in machine perfusion, which has led to the development of molecular approaches for assessing graft viability. The most prominent among these is flavin mononucleotide, which has emerged as a molecule to evaluate graft viability and also has the potential to predict graft survival. Cell-free microRNA, indocyanine green imaging, and transcriptomic analysis have also shown promise as viability markers (13).

The recipient's medical condition impacts the lower thresholds for graft volume in LDLT. Marubashi *et al.* demonstrated that the graft size necessary to prevent SFSS in patients with a MELD score of ≥18.2 is larger than that required for patients with a MELD score of <18.2 (14). Ikegami *et al.* showed that a MELD score of >19 and an end portal venous pressure of >19 mmHg were associated with severe SFSS after LDLT (15). These results suggests that the metabolic demands of recipients are not solely determined by graft volume. While MELD and portal venous pressure appears to reflect the metabolic demands of recipients, are these the only factors affecting these demands? To further advance recipient assessment beyond these studies, it would be valuable to explore the interactions between GRWR and recipient age, the etiologies of liver disease, platelet counts, and other relevant factors.

In conclusion, based on an analysis of 10,000 cases from the Japanese national cohort, Eguchi *et al.* reinforced the GRWR cut-off at ≥5 in pediatric cases and <0.6 in adult cases. This study provides an excellent foundation for further exploration of optimized donor-recipient matching in LDLT. Although GRWR is an older criterion, it remains a standard selection benchmark in LDLT. Future research should investigate the roles of functional graft volume and the functional volume required by recipients.

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