Editorial

Editorial on "Is there any correlation between liver graft regeneration and recipient's pretransplant skeletal muscle mass?"

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Liver regeneration is necessary for recovery following liver transplantation. The liver's regenerative capacity can, to a certain extent, alter the critical point between failure and eventual recovery of the transplanted liver (1). Poor liver function and failure of liver regeneration are most likely to be the direct result of liver injury factors. However, in living donor liver transplantation (LDLT), the impact of these factors on liver regeneration is diminished by standardized surgical procedures and detailed donor evaluation and selection. In the context of severe liver disease, the recipient's state is more important for liver regeneration (2).

Portal pressure reflects liver volume demand (3) and becomes a critical factor in controlling the speed and volume of liver regeneration (4). In hepatectomy and LDLT, extreme portal hypertension has a damaging effect and leads to impaired liver regeneration, known as small-for-size liver syndrome (5). In most cases, portal pressure can be tolerated and will be relieved gradually by liver regeneration. At this time, infection, immune damage, nutrition, and other recipient factors potentially affect liver regeneration (1,6). However, in current studies, the importance of these factors has not been determined.

Primary sarcopenia is a non-disease state of reduced body function and nutrition (7,8). Sarcopenia can also result from reduced nutrient and energy intake, anorexia, and neuroendocrine deregulation in liver diseases (9,10), and this is referred to as secondary sarcopenia (11). A dynamic reduction of muscle mass and muscle function is also included in the definition of sarcopenia. In most clinical studies, sarcopenia is regarded as a result of disease and is significantly associated with poor prognosis. In some pilot studies, nutritional supplements in liver cirrhosis patients have shown encouraging results (12,13), which may partly explain the causal relationship between sarcopenia and prognosis. The correlation between sarcopenia and adverse outcome in liver transplantation has also been described (14). An increased risk of infection and other postoperative complications is speculated to be the cause (15). However, how sarcopenia affects the recovery of liver graft remains unclear.

Pravisani *et al.* published a study in Hepatobiliary Surgery and Nutrition on the relationship between liver regeneration and sarcopenia in LDLT. The paper investigated the effect of liver regeneration on prognosis and the recipient factors affecting liver regeneration. Sarcopenia was found to be correlated with liver graft growth rate. Pretransplant malnutrition and competition for substrates were speculated to be reasons for this correlation. This provides a possible explanation for the relationship between sarcopenia and prognosis in liver transplantation recipients.

In their study, Pravisani *et al.* analyzed the data of 190 LDLT recipients from Nagasaki University Hospital. They found that graft regeneration rate (GRR) correlated with overall survival rate of recipients but did not correlate with graft loss. These findings indicated that liver regeneration might have delayed the recipient's recovery process and increased the risk of death during recovery. In the low-GRR group, a step-like decline in 2-year recipient survival

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suggested an adverse effect of GRR on long-term outcomes. However, there was no detailed analysis of complications or causes of death. Further, it remains to be determined whether liver regeneration was a contributing or concomitant factor to recipient death. It is not uncommon for transplant patients to die from causes other than graft failure, and these deaths may have been more closely related to sarcopenia.

The study reported a significant association between GRR after transplantation and pre-liver transplantation skeletal muscle index (SMI) in male recipients. This finding may have reflected the influence of poor nutritional and physical status on liver regeneration. However, there was no significant correlation between GRR and SMI in female patients, which was thought to be due to the poor correlation between sarcopenia and malnutrition in female patients. The authors speculated that fat loss may be the primary mode of nutrient consumption in female patients with liver disease. In this study, female recipients showed a slight increase in SMI after transplantation, which was markedly different from the decline in male recipients and consistent with the above hypothesis.

The authors also speculated that male liver transplantation candidates having a higher risk of poor energy and protein reserves may have explained why pre-liver transplantation SMI in men correlated with GRR. However, based on low muscle mass as defined by the Japan Society of Hepatology, the preoperative SMI of women in this study was not significantly higher than that of men. Thus, the hypothesis that men's preoperative energy reserve was lower than that of women was not supported by data. Other explanations for the difference in correlation between SMI and GRR between genders cannot be ruled out. For example, the differences between male and female patients in disease composition could be a potential reason.

By analyzing variation in SMI increase after transplantation (SMIv), the study found an independent negative association between SMIv and GRR in male patients, suggesting that there is nutrient substrate competition between liver regeneration and muscle growth. Nutritional factors have been speculated to be the primary mechanism for the association between SMIv and GRR. However, SMI is not a sufficiently reliable nutritional evaluation index on its own. Body fat content, BMI, and nutritional scoring system were not analyzed in the study.

Several potential causes for sarcopenia in patients with liver disease have been reported (11), including reduced glycogen storage in the liver, a decline in blood branched-chain amino acids (BCAA), change in levels of insulin-like growth factor-1 and testosterone, reduction of myostatin, increased production of reactive oxygen species, and persistent chronic inflammation, indicating that sarcopenia is more comprehensive than nutritional indicators alone. Thus, to explain the relationship between graft regeneration and sarcopenia solely from a nutritional perspective may not be comprehensive enough. All of the factors mentioned above may continue to exist or even intensify shortly after liver transplantation. Further, some of these factors were similar in males and females. Thus, while the development of sarcopenia may be similar in males and females, it may occur at different magnitudes. In the present study, low muscle mass as defined by the Japan Society of Hepatology was associated with a significantly lower GRR in both sexes, but there was no digital correlation. Standardized SMI data may be more effective in reflecting the relationship between SMI and GRR once variables are graded against a normal range.

Liver regeneration is essential for controlling portal hypertension associated with small-for-size liver syndrome in living liver transplantation. However, the graft volume (GV)/standard liver volume (SLV) ratio in this study was 36–47%, and thus the conclusions tend to describe a routine liver regeneration process after living liver transplantation, rather than regeneration in the context of small-for-size syndrome (5). The shear stress increased by portal vein pressure is an essential signal for liver regeneration (4). The study's significant negative correlation between GV/SLV and GRR reflects this problem to some extent. The relative "insufficiency" of liver volume can be considered the driving force leading liver regeneration, and this has been confirmed in previous studies (3). Some confounding factors may also interfere with interpreting results, such as the potential negative correlation between portal vein pressure, gastrointestinal function, and nutrition.

In summary, Pravisani *et al.* investigated the influence of liver regeneration on prognosis in their study. Based on the results of their data analysis, the authors speculated on the relationship between liver regeneration after transplantation with GV, portal pressure, and nutritional status of recipients. As an exploratory study, the results need to be further confirmed. A more comprehensive and detailed analysis, adjusting for the influence of multiple confounding factors and including a complete presentation of liver growth changes, may help clarify the problem.

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