The impact of ischemia-free liver transplantation to improve the prognosis of recipients using functioned marginal liver grafts

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Abbreviations

LT: Liver transplantation

HCC: hepatocellular carcinoma

ECD: extended criteria donor

SCS: static cold storage

NMP: normothermic machine perfusion
Liver transplantation (LT) has become widely acknowledged as the preferred life-saving treatment for patients with end-stage liver disease such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [1]. However, due to the scarcity of organs, not all patients on the liver transplant waiting list can receive the LT. The lack of liver grafts accounts for the major limitation of LT. [2]. Additionally, increased donor age and global burden of obesity are leading to an increase in marginal donors. The persistent gap between the need for organs and their supply has shifted attention to taking rescue strategies to utilize organs deemed marginal or unsuitable for transplantation [3].

In general, the criteria for marginal donor, that is, extended criteria donor (ECD), are as follows: donor age >65 years, ICU stay with ventilation >7 days, body mass index >30, steatotic liver >40%, serum sodium >165 mmol/l, serum alanine aminotransferase (ALT) >105 U/l, serum aspartate aminotransferase (AST) >90 U/l, serum bilirubin >3 mg/dl, and donation after cardiocirculatory death (DCD) [4]. It is well known that the current standard protocol, static cold storage (SCS) causes considerable damage to organs from ECD [5, 6]. The increase of ECD and marginal liver grafts is shifting the paradigm of SCS toward more complex organ preservation. This has led to the introduction of machine perfusion.

Therefore, recently, various clinical research has been focused on machine perfusion, especially normothermic machine perfusion (NMP), a new long-term preservation method. This method involves the liver being perfused with oxygenated blood. The use of NMP has led to positive results in LT using ECD [7, 8]. This NMP reduces ischemic time and cooling process.
and is reported to reduce graft injury by up to 50% despite 50% fewer organs being discarded [7]. Although the usefulness of NMP has been reported in many studies, there are still processes that can cause ischemia reperfusion injury. This is the ischemic time during organ procurement from the time of the aortic cross clamp to the time when the liver graft comes out and connects the NMP. With the machine perfusion method so far, blood interruption to the marginal liver graft could not be resolved. In contrast to traditional perfusion method (SCS or NMP), ischemia-free liver transplantation (IFLT) does not interfere with blood circulation to the liver graft during organ procurement, preservation, and transplantation [9]. As a result, IFLT can significantly reduce ischemic reperfusion injury.

In this issue of Clinical and Molecular Hepatology, Shuai Wang et al. demonstrated that ischemia-free liver transplantation (IFLT) improves the prognosis of recipients using functioned marginal liver grafts [10]. IFLT significantly improved the prognosis of functioned marginal liver graft (FML) patients compared to the SCS group. IFLT increased 90-day survival from 88.5% to 95.8% (p=0.220) and decreased mortality from 31.3% to 10.4% (p=0.006). Additionally, postoperative serum AST, ALT, and total bilirubin levels were lower in the IFLT group than in the SCS group. Additionally, although not statistically significant, the IFLT group showed a lower prevalence of PNF (0.0% vs 6.7%, P = 0.092) and EAD (29.2% vs 40.6%, P = 0.179) than the SCS group.

Recently, some investigations have demonstrated that inflammation resulting from pyroptosis contributes to ischemia-reperfusion injury in liver transplantation [11, 12]. As mentioned earlier, IFLT theoretically has no ischemic time because there is no interruption in blood circulation. As a result, pyroptosis was significantly inhibited in the IFLT group. The majority of pathways associated with inflammation were suppressed in individuals with IFLT, including cytokine signaling in the Immune system, Interleukin signaling, and the Fc gamma R-mediated
phagocytosis pathway. Additionally, the infiltration of NK cells was significantly lower in the IFLT group compared to the SCS group. IFLT has been shown to establish a microenvironment with characteristics that allow for less infiltration of NK cells. IFLT reduces liver injury by suppressing the infiltration of NK cells, thereby preventing IL-32-induced pyroptosis and the release of inflammatory factors (IL-1β and IL-18) in monocytes and macrophages.

However, the results of this study should be interpreted with caution due to several limitations. First, in this study, indications of SCS, NMP and IFLT were not provided in the study population. Additionally, because the numbers of the NMP and IFLT groups were too small, there were few statistically significant results showing the superiority of IFLT. And the NMP and IFML groups could not be directly compared because of this small number of patients. Second, some grafts with low quality tend to be evaluated under machine perfusion, which will lead to the protective effect of NMP being underestimated, even appears to an elevated EAD ratio. The conclusion about NMP should be drawn carefully. The protective effect of NMP on FML cannot be verified in this study. Thirdly, the application of IFLT may not always be easy in complex procurement processes. Usually, in deceased donors, not only the liver, lung, and heart but especially the pancreas can be harvested. There are no restrictions on NMP because it is applied to a liver graft that has already been harvested, but there is a possibility that IFLT may be restricted. Finally, although the pyroptosis-immune network has been studied, more detailed experiments must be performed to elucidate the mechanisms of liver injury in SCS to IFLT. This is because previously published studies on IFLT showed that the acute rejection rate in the IFLT group was higher than that in the SCS group [13].

In conclusion, the study by Shuai Wang et al. [10] represents that IFLT can improve LT outcome by preventing ischemic reperfusion injury during the entire LT process. There is no doubt that FML has a negative impact on outcomes after liver transplantation. Therefore,
finding ways to solve these problems in FML is an important issue in solving the organ shortage problem. Machine perfusion is the most useful method to address the problems of FML, and continued support and investment in research efforts to demonstrate the utility of IFLT will be needed.
References


