



Donor age predicts calcineurin inhibitor induced neurotoxicity after liver transplantation

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Liver transplantation is a curative therapy for many liver diseases. Grade of liver cirrhosis is classified with the Model for End-Stage Liver Disease (MELD) score and the Child-Turcotte-Pugh score. This last one employs five clinical measures of liver disease, including hepatic encephalopathy. After liver transplantation, immunosuppressive treatments are mandatory to obtain graft survival. The commonly immunosuppressive protocol includes calcineurin inhibitor like tacrolimus, corticosteroid, and mycophenolate mofetil.

After liver transplantation different type of complication may occur, surgical or medical complication. A related immunosuppressive complication is namely the calcineurin inhibitor-induced neurotoxicity (CIIN), and may occur in patients after liver transplantation within the first year after transplant. Many studies have analyzed risk factors to develop CIIN. MELD score and Hepatic encephalopathy have been described to be two of them. Complication after liver transplant have been described to be influenced by many factors as donor (age, macrosteatosis, donation after circulatory death) and recipient (severity of liver disease, previous myocardial dysfunction) features, and factors related to transplant operation (duration of cold and warm ischemia time, blood products transfusion and calcium requirements, surgical technique, hyperkalemia and hypothermia after graft reperfusion) (1). How do all these factors related to donor, recipient, and transplantation may affect the morbidity and the success of the transplant procedure? Candidates to liver transplantation can be patients with a low grade of cirrhosis but with hepatocellular carcinoma.

Contrariwise, most of them had severe liver cirrhosis, which affects all body performance (kidney, cardiac, pulmonary, muscles). Patients with high MELD or server sarcopenia due to malnutrition have more risk to develop complications after the transplantation. The quality of the graft depends on the donor's BMI, history of diabetes, hypertension, alcohol intake. At the time of organ harvesting, how the liver is perfused. Liver transplantation surgery may be affected by previous supramesocolic operations of the recipient like a liver resection. The technical difficulty for the arterial anastomosis can increase the warm ischemia time. Lué *et al.* have reported an interesting study entitled "Donor age predicts calcineurin inhibitor-induced neurotoxicity after liver transplantation" (2). The authors analyzed a cohort of 175 transplants from January 2010 to September 2016. The authors described CIIN in 21.1% of cases. They found to have more likely CIIN in patients with previous hepatic encephalopathy. This result confirms the previous literature (3). More interesting is the higher risk of CIIN according to the more upper donor age described by authors (P=0.002) within the CIIN group, the median age of 65 years old. Moreover, in logistic regression analysis, donor age was a risk factor associated with CIIN (P=0.027). The increasing number of candidates and the decreasing number of young donors push all transplant centers to use older donors moreover (4,5). Mediterranean countries like Spain or Italy have more and older population, and consequently, donor age is more often higher than 80 years old.

According to the marginal graft used for different transplantation strategy to improve early outcome have been described (i.e., temporary portocaval shunt during orthotopic liver transplantation with vena cava preservation) (6,7). More recently, a study from Pisa analyzed and explained the perioperative course of octogenarian and ideal young donors without finding differences (8). Delayed graft function wasn't significant different in this study; however, CIIN was not analyzed. Notwithstanding, many studies have been reported using machine perfusion to improve the graft in case of combinations of long ischemia time, advanced donor age, type of donor, and severe steatosis (9).

The preoperative condition of transplant candidates can be improved thanks to a hepatologist. It is now mandatory to have dietary management because of an inadequate nutritional intake is an essential cause of protein-energy malnutrition. When this malnutrition is associated with decreased physical activity, both conditions often lead to sarcopenia. On the other hand, in the case of the obese recipient, a restriction of excessive caloric intake is recommended. Moreover, exercise management during the waiting list time can increase skeletal muscle volume and strength and can improve insulin resistance in an obese patient. However, we will transplant high MELD patients for many years yet. Surgeons may enhance transplant conditions. Liver harvesting is now the real challenge for a transplant surgeon, improving the liver quality during the period from procurement to the implant. The only known way is the perfusion machine. Many types are present, and they allow us to improve the quality of hepatocyte. Eventually, CIIN is a severe complication after transplantation, but risk factors such as donor age may decrease in the next years.

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Footnote

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to declare.

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