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INVITED COMMENTARY

Utility and futility of early liver re-transplantation

Gabriela A. Berlakovich

Division of Transplantation, Department of Surgery, Medical University of Vienna, Vienna, Austria

Correspondence
Prof. Gabriela Berlakovich, Department of Transplant Surgery, University of Vienna, Währinger Gürtel 18-20 Vienna A-1090, Austria.
Tel.: 0043 1 40 400 4000;
fax: 0043 1 40 400 6872;
e-mail: gabriela.berlakovich@meduniwien.ac.at

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The numbers of liver re-transplantation present stable over time, both in Europe and United States, and the main indications for early re-transplantation still present hepatic artery thrombosis and primary nonfunction or dysfunction of the graft. Decades ago, this type of early graft failure was mainly caused by technical mistakes and lower experience in donor- and ischemia/reperfusion management. In contrast, nowadays, the reason for early graft failure is often attributed to the use of extended criteria donors. Transplant centers take this burden as they face the problem of rising numbers of patients on their waiting lists in contrast to a limited number of stable available donor grafts. To overcome this disparity, strict recipient selection criteria were defined for most indications as well as donor risk factors evaluated for expanding the donor pool.

On the one hand, even the use of old and very old donors and donors after cardiac death (DCD) cannot overcome this imbalance. Despite various published risk models, the difficulty in defining extended donor criteria for liver grafts [1–3] is not overcome sufficiently.

From the recipients' point of view, there is currently an ongoing discussion to identify those potential candidates who might be too sick for liver transplantation [4] as the expected outcome would be inferior compared with others. This approach might withhold individual patients the access of a life-saving therapy.

All these discussions occur under the pressure of organ shortage. The indication for early liver re-transplantation within the first year represents a special problem in this setting. Five-year patient- and graft survival rates are significantly reduced compared with first liver transplantation [5,6].

Rana *et al.* [7] examine re-transplantation rates and outcomes and identify three high-risk periods: the first week after primary transplant (POD 0-7), the first month (POD 8-30), and the first year (POD 31-365). Interestingly, independent risk factors for graft failure within these periods were different.

For the first week, cold ischemia time of >16 h, variceal bleeding within 48 h, and recipients being on life support were risk factors for re-transplantation. This combination identifies especially the high-risk recipient, and the recipient's profile determines the re-transplantation rate. About 20% of all re-transplants are performed within the first week, mainly for primary nonfunction or severe dysfunction or hepatic artery thrombosis.

Another 20% of re-transplants are within the second period and indicated by the same reasons of graft failure. The

use of a split liver graft, donor age >70 years, and variceal bleeding within 48 h represented the significant risk factors. Splitting a donor liver represents an additional trauma to the graft, an increased complication rate, and eventually a small-for-size syndrome. A liver graft from an old donor might be at risk of compromised quality and has decreased potential for regeneration of parenchyma. Both of these donor-derived risk factors are in accordance with published literature. In this period, the weight is more on the donor side and recipient risk factors become less important. The only recipient-derived risk factor in this period, variceal bleeding within 48 h, should be interpreted as surrogate parameter for impaired patients' condition.

Patients surviving the first month following liver transplantation usually show a rather stable condition. Therefore, it is not surprising that in the last period (POD 31-365), a further shift toward donor factors can be observed. It is well known that the use of DCD livers has a higher biliary complication rate in the meaning of ischemic bile duct lesions. The manifestation occurs usually 2-3 months after transplantation, and re-transplantation is the only treatment option. Comparable to the second period, an older graft (donor age >70 years) has a decreased potential of regeneration. Again, the only recipient-derived risk factor, age between 18 and 30 years appears of minor value and is just a reflection of clinician behavior of a more aggressively approach in younger patients. Therefore, in this last period, the re-transplantation rate is primarily dependent on the donor′s profile.

Like in most registry analyses, the publication by Rana *et al.* suffers from incomplete data entry. Interestingly, only 12% of recipients suffering from graft failure died from graft failure, 11% from infection but nearly 50% from "other" causes, which implicates some inaccuracy in data entry. Graft dysfunction will result in infection. A patient with graft dysfunction and consequently dying weeks or months later from sepsis or multi-organ failure should enter the database with graft-related cause of death.

As mentioned and discussed by the authors themselves, one of the study′s limitations represents the variable "Cause of graft failure," which had a data completeness of only 9.7%. Therefore, conclusions on cause of graft failure are impermissible despite the results were not surprising and in accordance with published literature. The relevance of this analysis from the UNOS database for Europe has to be validated. The re-transplantation rate is similar in both areas (5.5% UNOS vs. 7% ELTR) but both, donor- and recipient population are younger in United States compared with Europe [1,3], and therefore, risk factors might be different.

Last but not least the equitably allocation of a liver graft is more an ethical question than a medical, especially in the indication for re-transplantation. The main question is, if a patient was treated at an institution and treatment failed, has this patient acquired a right for further treatment even though using limited resources like liver grafts and an expected inferior outcome? Or is it justified refusing re-transplantation for this patient with the argument this patient had already a chance for a life-saving treatment and allocating the liver graft for primary transplantation with expected superior outcome?

Risk factor analyses of registry databases have a high scientific impact but constitute at most little help for the decision in daily clinical practice. Patients suffering from early graft failure represent a very inhomogeneous population with multiple recipient- and donor-derived risk factors in variable combinations. At the end of the day, the transplant team will have to decide, if an individual patient with early graft failure is accepted as candidate for liver re-transplantation or not.

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