Editorial

Qualifying the suitability of living donor livers for pediatric liver transplantation: are we doing the right thing?

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Over the last decades, liver transplantation has become the standard care for many forms of end-stage liver disease, both in adults and in children. The prognosis after pediatric liver transplantation (pLT) has steadily increased up to a patient survival at 5 years of 85% and an estimated graft half life of 31 years (1,2). In the early days of pLT, the transplanted organ originated from deceased donors. Since 1990, adult-to-child living donor liver transplantation (LDLT) programs have developed, which rapidly gained popularity, particularly in Europe and Asia (2,3). A major stimulus for LDLT has been the limited availability of deceased donors. The indications for liver transplantation have expanded, particularly for adult patients, at a higher rate than the availability of donor organs. Moreover, the quality of donor organs has steadily declined, resulting in a decreased utilization of livers from deceased donors for transplantation (4). The limited availability of qualified deceased donor livers has further stimulated LDLT: in Europe, for example, the percentage of living donor organs used for pLT increased from 7% before 2000 to 40% since 2010 (1). The decline in donor organ quality is not likely limited to deceased donor livers, exemplified by the projected exponential increase in non-alcoholic fatty liver disease (NAFLD) (5). Recently, Zhao and colleagues reported in this journal on the relationship between steatosis and idiopathic portal inflammation (IPI) in living donor livers and the clinical outcomes in pediatric liver transplantation (6).

Zhao *et al.* aimed to assess the prevalence of mild macrovesicular steatosis (5–30%) and mild IPI in donor livers which had been qualified for pLT and their association with the short- and long-term biochemical and clinical outcomes after pLT (6). The study was based on 305 in total 358 pLT procedures performed with a living donor in the Beijing Friendship Hospital between 2013 and 2018. The median post transplant follow up was just below 3 years. The median age of donors was 31.2 years, and their mean body mass index (BMI) was 22 kg/m^2. The mean age of the recipients was 1.0 years and the main indications for pLT were biliary atresia (70%) and genetic metabolic disease (23%). Living donor liver biopsy was obtained at the timing of LDLT and the donor liver histology thus did not play a role in the decision to qualify the graft. Rather, parameters of age, BMI, alcohol consumption, liver biochemistry and imaging were used for donor assessment. Macrovesicular steatosis was absent (0%) in 53% of the donor livers, 0–5% in 34% and 5–30% in 13% [scaling according to (7)].

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Only the group of 5–30% steatosis in the donor graft was considered the steatosis group. IPI, scaled according to Ishak modified histological activity score (8), was absent in 72% of the donor livers, mild in 26% and mild to moderate in 2% (the last categories were defined as the IPI group). The presence of steatosis and/or IPI in the donor liver was not associated with significant differences in serum alanine aminotransferase (ALT) or serum bilirubin in the recipient up to 1 month after transplantation. Similarly, no significant differences were found in short-term (<1 month) or long-term (>1 month) surgical or acute-rejection/infection related complications, nor in overall or graft survival, up to 5 years post pLT. Zhao and colleagues conclude that mild steatosis in living liver donors does not have a negative impact on the short- and long-term prognosis of the recipient in pLT. Although the authors are aware that the results do not reach statistical significance, they nevertheless suggest that mild IPI may negatively impact graft and overall survival, particularly when these grafts were transplanted in recipients with more advanced liver disease, quantified by a Pediatric End-stage Liver Disease score above 16.

The study by Zhao *et al.* demonstrates that excellent short- and longer-term recipient results can be obtained after LDLT in young children. The graft and patient survival rates at 5 years after pLT were well above 90%, illustrating the success of the LDLT program in their center, including the adequate selection of both recipients and living donors. The results also show that neither mild steatosis (below 30%) nor mild IPI negatively affects the patient and graft survival. Although these results are clearly supporting the cause for pLT and the use of living donors, several considerations warrant attention.

First, the living donors had been assessed for suitability by abdominal ultrasound and computed tomography, and were disqualified if there was "obvious fatty liver" upon either modality, until a considerable weight loss (by 8–10%) and the extent of fatty liver became mild or less. It was not reported how many of the donors had successfully undergone weight loss before ultimate qualification for living donation. Since the incidence of NAFLD [or, rather the new term, metabolic associated fatty liver disease (MAFLD)], increases, it would be valuable to know to what extent successfully losing body weight is indeed associated with justified qualification for living liver donation. The authors also reported 28 unqualified biopsies as exclusion for qualification, but this seems to contradict with statement that the liver histology was routinely obtained at the time of donor graft procurement. It may suggest that liver biopsies could also be taken before the LDLT in the assessment of qualification of the donor. The authors did not detail whether increased ALT levels could also be a reason for disqualification.

Second, although the single center number of LDLT procedures in pLT is high (n=305), this number as well as the still limited length of follow up (median: 3 years) may still hamper to draw definitive conclusions. Note that the absolute numbers of donor livers with steatosis or with IPI were only 41 and 85, respectively. Several of the results showed differences without reaching statistical significance. The conclusions on the "long-term" results would be helped by confirmation in other studies with larger group sizes and a longer follow up. In this respect, it should be underlined that protocol biopsies have indicated the development of fibrosis up to 10 years after pLT (9). It would be interesting to determine whether the incidence of graft fibrosis differs between the patients transplanted with a donor liver with or without steatosis or IPI.

In conclusion, Zhao and colleagues have provided valuable data for the assessment of potential living liver donors. The qualification threshold for donor livers that Zhao and colleagues used was associated with a very good post-transplant outcome, at least up to 5 years after pLT. Future studies are now indicated to confirm the present findings in (even) larger groups with longer follow up. Finally, the pLT field would additionally be helped by extending this type of analysis towards assessing pLT outcomes after transplantation of living donor livers with lower thresholds of qualification.

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