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Review

Hot topics in liver transplantation: Organ allocation – extended criteria donor – living donor liver transplantation☆

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Liver transplantation has become the mainstay for the treatment of end-stage liver disease, hepatocellular cancer and some metabolic disorders. Its main drawback, though, is the disparity between the number of donors and the patients needing a liver graft. In this review we will discuss the recent changes regarding organ allocation, extended donor criteria, living donor liver transplantation and potential room for improvement. The gap between the number of donors and patients needing a liver graft forced the transplant community to introduce an objective model such as the modified model for end-stage liver disease (MELD) in order to obtain a transparent and fair organ allocation system. The use of extended criteria donor livers such as organs from older donors or steatotic grafts is one possibility to reduce the gap between patients on the waiting list and available donors. Finally, living donor liver transplantation has become a standard procedure in specialized centers as another possibility to reduce the donor shortage. Recent data clearly indicate that center experience is of major importance in achieving good results. Great progress has been made in recent years. However, further research is needed to improve results in the future.

***Keywords*: Marginal liver; Liver transplantation; Living donor; MELD; Donor risk index**

1. Introduction

Over recent decades liver transplantation (OLT) has become the mainstay for the treatment of patients with decompensated liver cirrhosis, acute liver failure, hepatocellular cancer (within the Milan criteria) and some metabolic liver diseases. The major drawback of OLT is the scarce supply of donor organs in relation to the numbers of patients in need of OLT. According to the most recent UNOS Data 6650 liver transplants were performed in 2006 and at the same time 17,221 patients were listed on the waiting list. This disparity is certainly the biggest challenge for the transplant community. We have to ensure that the scarce organ pool is offered to the ones who need it most, while at the same time trying to close this gap in available grafts. In this review, we will discuss the changes that have taken place over the last few years regarding organ allocation and assess the recent changes in our understanding of extended criteria donors and living donor liver transplantation.

2. Organ allocation

The disparity between the number of donors and recipients which increased in most countries over the last decade, forced the transplant community to develop a system to prioritize the large number of

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Abbrevations: OLT, orthotopic liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; NHBD, non-heart beating donor; DCD, donation after cardiac death; PNF, primary non-function; IPF, initial poor function.

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potential recipients in relation to the available number of donors. In the US the allocation was initially based on hospital status of the patient, where patients in an intensive care unit received priority over patients hospitalized in a non-ICU unit and outpatients, and on the accumulated waiting time. With only three categories, the waiting time became of utmost importance in the allocation process, leading to the often, yet unnecessary listing of patients in the compensated stage just to start gaining waiting time [1]. Later the criteria were modified by first introducing minimal listing criteria. These criteria were based on the Child–Turcotte–Pugh (CTP)-score and required a minimum of 7 points for patients to be listed [2]. However, these criteria had no significant impact on the number of patients listed and waiting time remained the most important factor determining organ allocation. The fact that waiting list mortality did not correlate with waiting time but with disease severity suggested that waiting time should no longer be the most important criteria for organ allocation [3]. Whereas in the US organ allocation was always patient-based, in other countries such as Switzerland organ allocation was or still is center-based [4]. In some countries such as US and Switzerland, the transplant community was forced by law makers and politicians to rethink their allocation process [4,5]. In the new rules and regulations a major emphasis is placed on the patient's medical needs and less on local factors with the ultimate goal of reducing waiting list mortality. This search for a better allocation system led finally to the introduction of a modified model for end-stage liver disease (MELD score) by UNOS in 2002 to prioritize patients on the waiting list for liver transplantation. The MELD score is based on three objective biochemical parameters, which are readily available in each hospital. These variables are serum bilirubin, serum creatinine and the international normalized ratio (INR) of prothrombin time. Initially this score was developed to predict survival in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) [6]. This model was later validated in a large group of patients with chronic liver disease and the results suggested that this model can accurately predict 3-month mortality, independently of aetiology and complications of portal hypertension such as spontaneous bacterial peritonitis, hepatic encephalopathy and variceal bleeding. Therefore, the score could be used for organ allocation [7–9]. It was however recognized early on, that the MELD score does not accurately predict mortality of all diseases, which are currently treated by liver transplantation [10]. This is true not only for patients with hepatocellular cancer, but also for patients with familial amyloidosis, metabolic diseases and hepato-pulmonary syndromes. For these patients a "MELD score equivalent" must be assigned to assure timely transplantation.

2.1. MELD-based organ allocation

The introduction of the MELD score in the US was a success story and convinced other organizations such as Euro- and Swisstransplant to change to the MELD score as their liver allocation tool. A thorough analysis of the US data convincingly showed that the introduction of the MELD score was associated with a 12% reduction of new registrations to the liver transplant waiting list, a 3.5% reduction in waiting list mortality and identical posttransplant survival [11]. The survival benefit of liver transplantation was addressed in a large study by Merion et al. [12]. They analyzed waiting list and post-transplant mortality in cohort of almost 13,000 adult patients put on a US waiting list from 2001 to 2003. The mortality for transplant recipients with a MELD-score >18 was significantly reduced compared to patients not transplanted and this benefit continued to increase up to MELD 40. However, patients transplanted with a MELD score <15 did not have a demonstrable survival benefit within a 1 year posttransplant follow-up period. The MELD category of 15–17 represents a grey zone.

HCC is one of the diagnoses, where the MELD score does not reflect the urgency for transplantation. Therefore, it was important to assess, whether the arbitrarily assigned MELD score provided adequate timing before tumor progression precluded liver transplantation. It was reassuring to realize that the MELD system also had a beneficial effect on HCC liver transplant candidates [13]. In the MELD area, waiting time and dropout rate for HCC patients decreased, the number of patients transplanted with HCC increased and the overall survival remained unchanged.

2.2. Potential room for improvement

Although these data clearly show that the introduction of the MELD had a positive effect on organ allocation, the MELD score is not yet the holy grail of organ allocation [10]. The replacement of the CTP-score with the two subjective parameters ascites and encephalopathy through the MELD score with three objective laboratory parameters is certainly a step forward. However, the MELD score also heavily depends on the reproducibility of the laboratory determinations from institution to institution. It has been demonstrated that variability in the determinations of the laboratory values used to calculate the MELD score, most notably INR determination, could lead to changes in the MELD score of up to 20% or changes in the priority from the 58th to the 77th percentile [14]. Apart from the INR also the serum creatinine determinations can be affected by the type of assay used to measure it and especially the serum bilirubin concentration [15]. The interference from bilirubin results in lower serum creatinine concentrations

and is more pronounced with increasing bilirubin concentration, i.e. in patients with more advanced liver disease. Therefore, to reduce variability of laboratory parameters, standardizations of laboratory assays to measure INR and serum creatinine should be made mandatory by organ allocation agencies using the MELD system.

In an attempt to improve the MELD score, several studies suggested that serum sodium in addition to the MELD parameters might be an additional important parameter to predict waiting list mortality [16–18]. More recently, a prospective database was created to validate and refine the MELD model [19]. They observed a linear increase of mortality with decreasing serum sodium concentration and therefore incorporated serum sodium into a new MELD-Na score, which might provide a more accurate prediction of survival.

The MELD score only focuses on recipient characteristics and does not take into consideration any donor criteria (see extended criteria donors). Several recent publications however convincingly showed that quite a few donor factors such as age, gender, race, graft type (whole versus split liver graft), and ischemia time can affect posttransplant survival [20,21]. Since all these factors are not incorporated in the MELD score, it is not surprising that a recent systematic review of MELD score concluded that this score is not able to predict mortality after liver transplantation [22].

Further refinements of the system, such as standardization of laboratory procedures, incorporation of new parameters such as sodium and maybe donor and recipient matching might further improve the allocation process and optimize justice and utility at the same time.

3. Extended criteria donor

As mentioned earlier, a major challenge for the transplant community is to develop strategies to close the gap between the number of patients in need of a transplant and the number of available organs. Among others, this includes increasing the donation rate, developing living donor liver transplant programs or new surgical techniques such as split liver transplantation and finally using organs that were previously thought to be associated with an unacceptably high risk of primary nonfunction (PNF) or initial poor function (IPF), so called extended criteria donors [23]. An accepted definition of extended criteria donor livers has not yet been established by the liver transplant community. However, several risk factors (Table 1) that are associated with an increased rate of PNF or IPF have been identified [24].

Table 1
Significant donor risk factors

Significant donor risk factors	5 Donor and 2 transplant risk factors identified in the US [33]		6 Donor and 1 transplant risk factor identified in the UK [47]	
	Risk factor Reference value	Increased risk of graft failure Relative risk	Risk factor Reference value	Increased risk of graft failure Relative risk
Age	Age <40	61–70: 1.53 >70: 1.65	Age	Increase by 1.05 per decade
Race	White	African American: 1.19	White	Non-white: 2.17
Size	Height	Increase by 1.07 per 10 cm decrease in height	nr	
Cause of donor death	Cause of donor death: Trauma	CVA[a]: 1.16 Other[b]: 1.20 DCD[c]: 1.51	nr	
Type of graft	Full graft	Partial/split: 1.52	Full graft	Reduced/split: 1.93
BMI	ns		BMI	Increase by 1.01 per unit increase in BMI
Graft appearance	No data		Normal	Suboptimal: 1.31
Diabetes	ns		No diabetes	Diabetes: 1.41
Transplant risk factors				
Cold ischemia time	Cold ischemia time	Increase of 1.01 per hour	Cold ischemia time	Increase of 1.02 per hour
Sharing outside local area	Local area	Same region: 1.11 National: 1.28	nr	

ns, not significant; nr, not reported.
[a] Cerebrovascular accident.
[b] Cause of death not trauma, cerebrovascular accident or anoxia.
[c] Donation after cardiac death.

3.1. Donor age

Donor age steadily increased over recent decades. In 1994, only 20% of deceased donors were 50 years or older. This precentage increased by more than 150% in the year 2004 [25–27]. Although some studies suggested that donors older than 50 years without additional risk factors have similar outcomes compared to younger donors [28–32], more recent studies using the large databases of either SRTR/UNOS or ELTR clearly identified donor age as an important risk factor for poor outcome after liver transplantation [20,21,33].

3.2. Donor gender, weight, height and race

Even though the donor gender has been identified as a risk factor for post-OLT outcome in some studies [21], this could not be confirmed by others [33]. Race, however, consistently seems to affect recipient outcome [21,33]. Interestingly, of the two parameters reflecting donor size, only height but not weight was independently associated with recipient outcome [33].

3.3. Cause of donor death

In the early years of liver transplantation the typical cause of death of an organ donor was related to cerebral trauma. In more recent years cerebral trauma as a cause of death of organ donors has gradually decreased, while cerebrovascular causes increased [34]. According to the study by Feng et al. cause of death other than trauma was associated with a 16% (cerebrovascular accident) and 20% (other causes) increased risk of graft failure, respectively [33].

The success of renal transplantation from non-heart beating donors (NHBDs) also referred to as donation after cardiac death (DCD) has led to a renewed interest in the liver transplant community as a potential way to increase the donor pool [35–37]. NHBDs are divided into controlled and uncontrolled group in order to underline differences in clinical practice, graft outcome, ethics and future potential [38]. Controlled donation occurs in an intensive care unit in a controlled environment, whereas in uncontrolled donation the donor death occurs either outside the hospital or in the emergency room following an unsuccessful attempt of resuscitation [38]. In controlled NHBD warm ischemia time can be accurately assessed, cold ischemia can be minimized and it is estimated that the donor liver pool could be increased by as much as 20% [39]. The results of controlled NHBD approach those of heart-beating-donation, but vascular and biliary complications might still be higher for a recipient of a DCD graft [40–42]. In addition, in the large analysis of donor risk factors by Feng et al. DCD was associated with a 51% increased risk of graft failure [33]. New techniques for liver procurement, which are currently tested in experimental settings, are urgently needed to optimize DCD [43].

3.4. Graft steatosis

Considering the current epidemic of adipositas in developed countries, it is obvious that more and more liver grafts will be steatotic. The transplant community will be forced to provide guidelines on how to use these grafts safely. Steatosis has been traditionally classified according to morphology as macrovesicular or microvesicular and according to quantification as mild, moderate or severe if less than 30%, 30–60% or more than 60% of hepatocytes are affected [44,45]. The assessment of a donor organ is one of the most difficult tasks for the transplant team. While macroscopic examination appears to be fairly reliable in determining the presence of severe grades of steatosis, it fails to detect moderate and mild degrees [46]. Although macroscopic inspection is very subjective, in a recent publication in abstract form, inspection of the graft (suboptimal versus normal) was identified as a significant risk factor for graft loss [47]. When steatosis is suspected at inspection, 38% of liver transplant surgeons in the UK and 47% in the US proceed to histological examination of the graft. In spite of the low overall positive predictive value of macroscopic assessment, 50% of UK transplant surgeons never integrate histopathologic assessment into their decision-making process [48]. While the same survey indicated a much higher use of biopsies in the US, current OPTN data (as of April 14, 2006) reveal that only 27.8% of all 7593 cadaveric livers considered for OLT in 2005 were actually biopsied [49]. Although microscopic examination remains the "gold standard", different tissue processing and staining techniques can affect detection and grading of steatosis [50]. Data on the clinical relevance of fat detected by more sensitive stains are still lacking and there is currently no consensus on how to assess the degree of steatosis in a liver graft.

There is no question that mildly steatotic grafts can be accepted for liver transplantation [49]. In contrast, assignment of moderately steatotic grafts (between 30% and 60%) is still controversial. There is current agreement that moderately steatotic grafts qualify as extended criteria grafts because they have been associated with poor clinical outcome, particularly when associated with additional risk factors [46]. While some investigators have reported increased rates of PNF (13% versus 3%) [51], others found identical 1-year graft and patient survival when transplanting livers with moderate steatosis and non-fatty livers, respectively [46,52–54]. Recent studies therefore conclude that grafts with moderate steatosis can be safely used in low risk patients, whereas they should be discarded for recipients with a high MELD score [49,55]. However, primary dysfunction was unanimously more common in the

steatotic groups. Unfortunately, the impact of primary graft dysfunction on long-term graft outcome is still unclear.

A recent report from our center opened the debate about the use of severely steatotic grafts [56]. In a case control study of 20 patients with severely steatotic grafts (90% liver steatosis) and 40 matched controls 60-day mortality (5% versus 5%) and 3-year patient survival rate (83% versus 84%) were comparable between the control and severe steatotic group. Our study challenges the dogma that liver grafts with severe steatosis should be discarded for all recipients, but this finding certainly needs to be confirmed by other studies.

3.5. Type of graft

Although split liver transplantation is well established in pediatric patients, its role in adult patients is still controversial. A recent match pair analysis of patients after whole versus split liver transplantation using an extended right liver lobe found no difference in neither short nor long-term morbidity or mortality [57]. Others, however, showed an inferior graft survival rate for recipients of the left graft [58]. This is supported by the recent analysis of the large SRTR database, where split or partial grafts were associated with 52% higher risk of graft failure [33].

3.6. Cold ischemia

One of the major reasons for graft dysfunction is undoubtedly ischemic injury to the graft. More than 14 h of cold ischemia has been consistently associated with an increased preservation damage associated with a prolonged postoperative course, biliary strictures and decreased graft survival [59–61]. Accordingly, the risk of graft loss increases by 1% for each additional hour of cold ischemia [33].

3.7. Other factors

The role of several other risk factors identified in different studies such as obesity, elevated liver functions tests, hypotension or increased vasopressor use and hypernatremia [24] is less clear, as they were not associated with an increased risk of graft failure in the most recent study [33].

3.8. How to translate this into clinical practice

In a large retrospective study by Feng et al. including data from more than 20,000 donor from the US Cox regression models identified 5 donor characteristics (Age, race, donor height, donor death (Cerebrovascular accident (CVA), causes of death other than trauma, stroke or anoxia and donation after cardiac death (DCD)) and type of graft (partial/split graft)) that independently predicted a significantly increased risk graft failure [33] (Table 1). In addition, they recognized two transplant-related factors (cold ischemia time and sharing outside of the local donor service area), which were also significantly associated with graft loss [33]. All these factors were used to generate a donor risk index, which is directly related to a predicted rate of graft survival. In a very similar study from the United Kingdom, which is so far only published in abstract form, Dawwas et al. also identified 7 slightly different risk factors for graft loss [47] (Table 1). These could also be used to calculate a donor risk index. In the UK setting, the UK donor risk score outperformed the US donor risk score [47]. However, both scores need to be externally validated in other populations before firm recommendations about their use can be made. Nevertheless, together with the MELD model, which assesses the risk of death of the recipient on the waiting list, we now also have tools, that provide us with prognostic information about the graft. Unfortunately the donor risk index is only an estimate for the average patient on the waiting list and not yet applicable to specific patient population. So far, only the Markov models suggest that for patients with MELD score greater than 20, immediate transplantation even with grafts that carry a risk as high as 50% for a primary graft failure is still associated with a survival benefit [62]. However, we eagerly await reports which are based on real data and not on modeling approaches.

4. Living donor liver transplantation (LDLT)

Living donor liver transplantation (LDLT) has been one of the other options to expand the scarce donor pool [63,64]. Initially, the recipients in LDLT were mostly children, but with growing expertise with right lobe donation, LDLT today is also a valuable option for adult recipients [65].

4.1. Donor selection

Appropriate donor evaluation is one of the most crucial parts in LDLT [65]. The goal of the evaluation process is to exclude donors with an increased risk for morbidity and mortality, while at the same time assuring that a suitable graft for the recipient can be obtained. In a recent large retrospective study from the US the characteristics and acceptance rate of donor candidates ($n = 1011$) was evaluated over a period of 5 years [66]. In total, the acceptance rate for donor candidates was 40%. It is interesting to note that donor acceptance rate dropped significantly from 47% (1998–2000) to 35% (2001–2003). Similar data have already been reported from single center experiences, with acceptance rates as high as 63% for the period 1997–2001 compared to only

36% for the period 2002–2005 [67]. The reason for this decline is not entirely clear, but could be related to the highly publicized donor death in the US or differences in the allocation process after introduction of the MELD system. Even higher donor rejection rates are reported from Europe (86%) [68], whereas this rate is considerably lower in Japanese centers [69,70]. The strongest predictors of donor acceptance in the recent US study were in decreasing order of significance: center of evaluation, donor BMI, year of evaluation, recipient MELD-score, days from listing to first-donor evaluation, recipient age, donor–recipient relatedness and donor age. Surprisingly, only donor BMI, donor age and relatedness were donor-specific factors influencing the acceptance rate, whereas the strongest predictor was neither donor nor recipient-related. This suggests that other currently less well defined "local" factors play an important role in the donor acceptance process.

4.2. Donor outcome

The goal of the donor evaluation process is to assure a safe outcome for the donor. But even with the best evaluation process complications and even death cannot be completely avoided. Currently, over 3500 adult to child and over 2500 adult to adult living donor liver transplantations have been performed worldwide. In a recent systematic review of more than 300 articles covering approximately 6000 LDLT procedures, it is estimated that the donor mortality is approximately 0.2% [71]. Mortality is higher for adult to adult (0.24–0.4%) compared to adult to child donation (0.09–0.2%). This is explained by the fact that adult to adult donation mostly encompasses a right lobe and adult to children mostly a left lobe donation. Left lobe donation has been associated with a lower mortality (0.05–0.21%), compared to right lobe (0.23–0.5%) [71].

Reporting of morbidity is unfortunately not standardized, explaining the huge range from 0% to 100% with an average morbidity of 16.1% [71]. The most common complications are biliary complications and infections. The median biliary complication rate was 6.2% (range: 0–38.6%). Infections were mostly wound or urinary tract infections with a median rate of 5.8% (range 0–28.6%). To better standardize the reporting of donor morbidity the Vancouver Forum on the care of the live organ donor recently proposed to use the Clavien or modified Clavien system to record and grade live donor complications by severity [72–74]. The recently introduced modified classification still mostly relies on the therapy used to treat the complication but four important modifications to increase its reliability and potential use in the surgical literature were introduced [73] (Table 2). First, life-threatening complications requiring an intermediate or intensive care management (IC/ICU) were differentiated from complications treated on the ward. Secondly, complications involving the central nervous system (e.g. ischemic stroke, brain hemorrhage, subarachnoidal bleeding) were also considered as grade IV complications. Third, the length of hospital stay is no longer considered in the ranking of complications and fourth, the presumed long-term consequences of a complication are integrated in the new classification. This new classification was used to retrospectively evaluate the complication rate from two large healthcare registries involving 433 right and left lobe donors from 13 centers in the US between 2001 and 2005 [75]. There was one perioperative death (0.23%) and the overall complication rate was 29.1%. The major complication rate (Clavien grade $\geqslant 3$) was 3.5%. Risk factors for lower overall complication rate were center living donor volume (OR = 0.97; 95% CI = 0.95–0.99) and ratio of living donors to all donors (OR: 0.94, 95% CI = 0.92–0.99). The only risk factor associated with major complications was donor age over 50 (OR: 4.25, 95% CI = 1.22–14.97). In our current experience involving 19 donor operations, we observed one major complication (Grade 3a), three grade I and II each and in 12 cases the outcome was completely uneventful (Clavien et al., unpublished data).

In contrast to somatic complications, psychiatric complications of the donor are not nearly as well stud-

Table 2
Classification of complications (for details see Ref. [76])

	Dindo et al. [73]
Grade 1	Any deviation from normal course requiring no pharmacologic treatment except: antiemetic, antipyretic, analgesics and diuretics
Grade 2	Requiring pharmacologic treatment with other than those allowed for grade 1
Grade 3	Requiring surgical, endoscopic or radiological intervention (a) not under general anesthesia (b) under general anesthesia
Grade 4	Life-threatening complications requiring ICU management (including central nervous system complications) (a) single organ dysfunction (b) multiorgan dysfunction
Grade 5	Death of patient

ied. The Adult to Adult living donor liver transplantation cohort study (A2ALL) recently reported the type and prevalence of severe psychiatric complications in 392 donors enrolled in the A2ALL study [76]. During a median postoperative follow-up of 6 months (range: 3 days–5.6 years) 16 patients (4.1%) developed one or more psychiatric complications, including 3 severe (suicide, dead after accidental drug overdose and suicide attempts). All recipients of the three donors with severe complications were alive and well at the time of these events. So far, the focus has centered on surgical complications in the early postoperative period, but these data clearly underline the need for a careful psychiatric predonation work-up and also for a regular long-term follow-up of donors to fully appreciate the full burden of complications associated with living donation.

4.3. Recipient selection

All recipients should be listed on a national waiting list and indications for LDLT should be the same as those established for deceased donor liver transplantation. Therefore, every patient eligible for cadaveric liver transplantation is also a candidate for LDLT. In addition, the Vancouver Forum stated that the expected graft and patient survival of LDLT should be approximately the same as for a recipient of a deceased donor transplant with the same disease [74]. It has been recognized early on that patients with severely decompensated liver disease do not tolerate LDLT very well [77]. In patients with chronic liver disease and severe decompensation (MELD > 30) the long-term mortality following LDLT (57%) was significantly higher compared to deceased donor transplant (18% historical control) [78,79]. Therefore, it has been recommended not to offer LDLT to donors with a MELD score >25 [80]. This policy is also reflected in the recent report from the A2ALL consortium, which retrospectively analyzed the outcome of 384 adult to adult living donor liver transplant recipients [81]. In this report the mean MELD score at the time of transplant was 15.6 ± 6.9 (range 6–40), compared to a mean MELD score of 22 in deceased donor liver transplantation. Only 4% had a MELD score greater than 30 points and 4% were patients with fulminant liver failure.

The major advantage of LDLT is to shorten waiting time. Therefore, patient groups with an urgent need for liver transplantation or whose disease severity is not well reflected by the MELD score seem to be prime candidates for LDLT [80]. Part of the first group are patients with HCC, who could benefit from fast-track transplantation, even with current prioritization through the corrected MELD score. To the latter belong patients with mostly cholestatic liver disease and severe pruritus or patients with ascites and/or encephalopathy, but still well-preserved liver function.

4.4. Recipient outcome

Although LDLT recipients have a shorter waiting time, initial reports suggested that LDLT recipients had a higher graft failure rate (hazard rate 1.66) [82] and a 10% lower graft survival rate after 2 years associated with a 60% higher likelihood of graft loss [83]. However, a recent retrospective analysis of the A2ALL study group clearly showed, that graft failure rate correlated with experience; i.e. centers with more than 20 LDLT had a significantly lower graft failure risk [81]. Accordingly, more recent studies reported similar patient survival rates among living donor and deceased donor liver transplant recipient [84]. Reduced waiting time is the big advantage of LDLT and this obviously could also impact on patient survival. This was addressed in a recent study by Shah et al. that analyzed the outcome of LDLT from the time of listing and not from the time of transplant [85]. In their large study with 144 LDLT and 350 DDLT recipients, they could show that LDLT recipients had a significant survival advantage over DDLT after 1 year (90% 1-year survival compared to 80%). Direct comparison of survival rates is, however, problematic, since MELD-scores at the time of transplant are in general significantly higher in the DDLT group compared to the LDLT group. This was also true for study by Shah et al. Although MELD-scores at the time of listing were similar, the LDLT group had a significantly lower MELD at the time of transplant. Very similar results were obtained by a recent study of the A2ALL study group [86]. In their analysis, the relative mortality risk of LDLT was only 56% compared to DDLT ($p < 0.001$). As previously reported in other studies, the benefit of LDLT depended on experience and was lower (Hazard ratio: 0.83) in the less experienced period (<20 LDLT) compared to the more experienced period (Hazard ratio: 0.35, $p < 0.001$). In this study, early re-transplantation (3 weeks) was necessary in 1.1% of DDLT recipients and 7.8% and 3.6% of LDLT recipients in the less and more experienced period, respectively.

4.5. Recipient complications

Most complications are similar in LDLT and DDLT recipients. However, it has been consistently shown that biliary complications are more frequent in LDLT compared to DDLT recipients, occurring still in 24–67% (for review see ref [87]). Possible risk factors associated with an increased risk of postoperative biliary complications included multiple ductal openings [88], a high preoperative model for end-stage liver disease score ($\geqslant 35$) [89] and older donor age and previous history of a bile leak [90]. Whereas initially more Roux-en-Y (R–Y) anastomoses were performed, today most authors would agree that duct to duct anastomosis is safe and has the

advantage of providing access for future endoscopic therapy in cases of leak or stricture. This increased complication rate also leads to higher hospitalization rates in LDLT recipients [91]. In the first year the increased number of hospitalizations was due to biliary and non-biliary complications, whereas after the first year, these were mostly because of biliary complications.

4.6. LDLT in patients with chronic hepatitis C

Liver cirrhosis due to chronic hepatitis C is the most common indication for liver transplantation in most countries. Therefore, the outcome of this patient group after LDLT was of special interest. Initial reports suggested that HCV recurrence in LDLT recipients might be faster and more severe, whereas these differences were no longer consistently observed in more recent studies (for review see ref [92,93]). Comparison of the results is however difficult, since the definition of HCV recurrence, the use of protocol biopsies and antiviral treatment before and after transplantation differ widely between studies. The large retrospective analysis by the A2ALL study group of 181 living donor liver transplant (LDLT) recipients and 94 deceased donor liver transplant (DDLT) recipients with chronic hepatitis C showed a 3-year graft and patient survival of 68% and 74% in LDLT compared to 80% and 82% in DDLT, respectively [94]. The difference for graft survival but not patient survival being significantly lower in the LDLT group compared to the DDLT group ($p = 0.02$). However, if adjusted for experience of the center (>20 LDLT) 3-year graft survival for DDLT and LDLT with more than 20 procedures was no longer significantly different (80% versus 79%). Predictors of graft loss beyond 90 days included LDLT $\leqslant$ 20 (Hazard ratio = 2.1, $p = 0.04$), pre-transplant hepatocellular carcinoma (HCC) (HR = 2.21, $p = 0.03$) and severity of liver disease, i.e. model for end-stage liver disease (MELD) at transplantation (HR = 1.24, $p = 0.04$).

4.7. Conclusions

The introduction of the MELD scoring system undoubtedly improved the allocation process. It will be interesting to see whether the combination of the MELD score with a donor risk index might further refine the liver allocation process. In this regard a better understanding of the impact of extended criteria donors and especially steatosis on outcome will be crucial. A prerequisite to better understand the impact of graft steatosis on outcome will be to obtain routine donor liver biopsy at the time of harvest. Unfortunately, these data are currently lacking in most large donor databases. It has become clear that experience in LDLT significantly affects outcome, therefore it might be advisable to restrict LDLT to a limited number of centers.

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