

Utilization of extended donor criteria in liver transplantation: a comprehensive review of the literature

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Abstract

Organ shortage has driven many transplant programs to extend their criteria to accept donors. The goal of the present work is to further characterize the most important extended donor criteria (EDC) in liver transplantation and to identify factors that impact outcomes for this type of grafts through a comprehensive review of the most recent findings and current opinions. Age, steatosis, positive viral hepatitis serology, intensive care unit stay, and history of malignancy in donor have been the matter of substantial debate in recent years and are therefore discussed in further detail here. Cold and warm ischemic times have also been discussed separately as they have been identified as important independent risk factors for mortality. The use of grafts with EDC provides an immediate expansion of the donor pool. However, in order to optimize effective utilization of EDC, attempts should be made to carefully match the most appropriate graft-recipient pair.

Keywords: liver transplantation; extended donor criteria; graft survival; patient survival; donor age; steatosis; hepatitis; malignancy; ischemia time

Introduction

The gap between the number of available organs and the number of patients waiting for liver transplantation has continued to widen over the past decade, with an increasing individual waiting time and patients dying on the waiting list before transplantation [1]. Organ shortage has led many transplant centres to pursue strategies to increase the donor pool including the use of living donors, split livers, and domino transplants, as well as to extend the criteria for organ acceptance.

The concept of accepting extended donor criteria (EDC) for liver transplantation becomes better characterized. The Bundesärztekammer [German Medical Association] has identified the following donor characteristics as EDC: age >65 years, intensive care unit (ICU) stay and ventilation support >7 days, body mass index (BMI) >30, biopsy proven steatosis >40%, peak serum Sodium >165 mmol/l, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×normal, serum total bilirubin >3 mg/dl, positive serology for viral hepatitis (hepatitis B virus (HBV) surface antigen -HBsAg-, hepatitis B virus core antibody -antiHBc-, or hepatitis C virus (HCV) antibody -anti HCV-positivity), sepsis with positive blood culture, meningitis, history of extrahepatic malignancy, and previous drug abuse [2]. These factors have been presumed to increase the risk of initial graft dysfunction [3,4], and their combination is thought to be additive on graft injury (Figure 1) [5–7]. However, there have been attempts to evaluate the actual degree of risk that EDC grafts may impart to a recipient, to adopt adequate measures to maintain good graft and patient results, and to establish the exact cut-off point for the acceptance of such grafts in order to identify the already existing absolute risk factors for poor graft function. The aim of the present work has been to further characterize the most important EDC through a comprehensive literature review, to address the actual risks that EDC pose to graft function, and to introduce the pre-emptive measures to eliminate the risks of EDC when possible.

Donor characteristics that are considered to be potentially more detrimental for transplantation outcome have changed over time. Recent multivariate analyses of large national and single centre series have failed to demonstrate factors such as donor female sex, obesity, elevated liver function tests, hypotension/increased pressor use, and hypernatremia as independent risk factors for poorer outcome [8–10]. However, there are some specific EDC that need especial considerations in order to maintain

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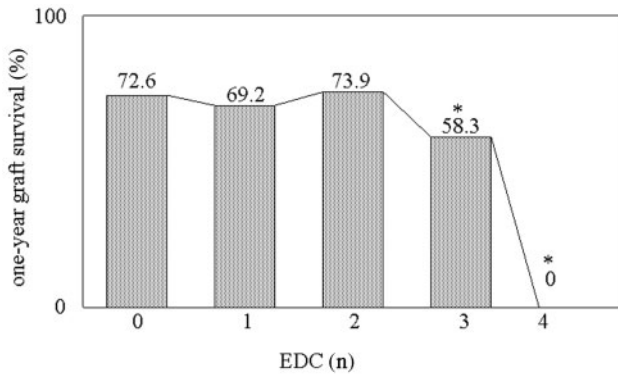


Fig. 1. Cumulative effect of extended donor criteria (EDC) on one-year graft survival. Diagram depicting one-year graft survival after transplantation of livers with EDC from 422 consecutive liver donors (1992–2004) in Baden-Württemberg, Germany. Two hundred and twenty eight livers were investigated to have 1, 2, 3, or 4 EDC. Grafts with ≥ 3 EDC had significantly lower 1-year post-transplant survival ($P < 0.05$). Graft loss included primary nonfunction, chronic rejection, and recipient's death. All grafts with 4 EDC were lost within 1 year. Modified from Fischer-Fröhlich *et al.*, Deutsche Stiftung Organtransplantation (DSO), Stuttgart, Germany, 2006. * $P < 0.05$; EDC: Extended Donor Criteria.

acceptable outcomes. The following discussion focuses on these more important criteria among all factors identified as EDC.

Donor age

Over the last decade, using of cadaveric livers from older donors has been remarkably accelerated. According to the United Network for Organ Sharing (UNOS), the annual number of donors >65 years has been increased about 14-fold from 1991 to 2001 [11]. Within the same time period, the European Liver Transplant Registry (ELTR) has reported an increasing percentage of donors ≥ 60 years from 2% to 20% [12], as well as doubling the median donor age from 25 to 50 years [13]. This donor category has been identified as the most important factor to increase the number of cadaveric liver transplantations [14].

Physiological and morphological studies suggest that, compared to other organs, the liver seems to age slowly. Routine liver function tests do not show age-associated changes and even the synthesis rate and concentration of albumin seems to be stable into old age. Hepatic flow decreases about 35%–40% and bile flow about 50%, reflecting at least in part, impairment of energy-dependent and microtubule-dependent transport processes. The cytochrome P450 content of liver specimens is recently reported to decline from the age of 40 to 69 years by 16% and further decline by 32% after age 70 [15]. Ultrastructural changes in the aging liver include pseudocapillarization of the sinusoidal endothelium, defenestration with reduced porosity, thickening of the endothelium, infrequent development of basal lamina, and only minor collagen deposits in the space of Disse. These changes may restrict the availability of oxygen and other substances [16].

Furthermore, preperfusion biopsies of livers from donors >60 years show higher rates of moderate to severe microvesicular steatosis compared with those from <60 year-old donors, as well as higher values of bilirubin and prothrombin time [17]. Therefore, older livers may be more susceptible to endothelial cell injury from cold ischemia [18,19], which may be potentiated by the more prevalent steatosis found in livers of the elderly, decreased ATP synthesis after reperfusion, which may decrease regenerative capacity and synthetic function, and delayed function with a notable cholestatic pattern after implantation [20]. A recent study has shown that in the elderly, the liver may not be morphologically smaller, but the hepatocyte volume decreases, i.e., it has fewer larger hepatocytes histologically [21]. This problem may result in a physiologically mismatched graft despite its size being appropriate.

Regarding post-transplant complications and survival, findings are not unanimous in the literature. On one side, old livers have been reported to be more susceptible to rejection episodes, biliary complications [22], increased risk of vascular complications due to arteriosclerosis of the hepatic artery [23], and greater risk of transmission of occult tumours [24,25]. A prospective cross-sectional study of 270 patients with a first functional liver graft at 10 years of follow-up undergoing liver biopsies has identified donor age as a major independent determinant of the long-term histological prognosis of liver grafts [26]. A review of the liver transplantation database of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has declared the donor age >59 years as one of the three independent clinical characteristics most associated with resource utilization [27]. On the other side, others have observed no significant increase in the incidence of acute rejection, nonischemic biliary stenosis, FK-506 and cyclosporine toxicity, renal failure necessitating dialysis, level of immunosuppressive drugs [20], and intensive care unit or total hospital stay [28]. Regarding increased vascular complications, some argue that even if the celiac axis may be involved with atherosclerosis [29], the hepatic arterial tree is generally spared even in the elderly [30]. Persistently elevated gamma-glutamyl-transpeptidase (GGT), alkaline phosphatase, and total bilirubin have been reported to almost resume to normal values at 12 months after transplantation [28]. Reports on patient and graft survival following transplantation of older donor livers are also highly variable. A review of larger multivariate analyses including older donor age performed after year 2000 shows that while some observed significantly lower short term graft survivals with older livers, others have found significant differences only in longer terms, or no differences at all (Table.1) [10,20,22,28,31,32]. This discrepancy may be, at least in part, due to different selection policies regarding older donor livers at different centres.

The association between the use of older donor livers in recipients with hepatitis C virus (HCV) and

Table 1. Multivariate regression analysis on the impact of donor age >60 years

Author, TPL center, year	Cut-off age (CA)	<i>n</i> *		PNF [%]		Graft survival [%]												
						<1 year		1 year		2 years		3 years		5 years				
		>CA	<CA	>CA	<CA	>CA	<CA	>CA	<CA	>CA	<CA	>CA	<CA	>CA	<CA			
Moore <i>et al.</i> Vanderbilt 2005	60 year	35	399												35	75		
Neipp <i>et al.</i> Hanover 2004	60 year	67	1141	12	?			68	69	65	66				<0.001	53	60	
Tector <i>et al.</i> Indiana 2006	60 year	60	511	3	0.2	80	91.3	67.4	84	61.5	77.6						<i>ns</i>	
Markmann <i>et al.</i> UCLA 2001	65 year	56	947					0.03		0.03					62	75		
Busquets <i>et al.</i> Barcelona 2001	70 year	21	327	5	2	1m: 81	89								0.006		25	59
				<i>ns</i>		<i>ns</i>		6m: 56	81								<0.001	
Nardo <i>et al.</i> Bologna 2004	80 year	30	60 [‡]	0	2	3m: 96.7	90					?	?	?	?	?	?	?
				<i>ns</i>		<i>ns</i>								<i>ns</i>		<i>ns</i>		<i>ns</i>
						6m: 90	90											
						<i>ns</i>												

TPL, transplant; CA, cut-off age; PNF, primary nonfunction; yr, year; m, month; U, university; *ns*, not significant.

Survival analysis for donor age > 60 years performed after 2000. *The patient population above the cut-off age versus the population below the cut-off age. A p value is provided where applicable. †Not provided by authors. There were 2 PNFs within the donor groups of 'older than 60 years' versus 1 PNF in 'standard donors'. The difference seems to be significant. However, this difference may be attributable to long warm and cold ischemia times in the former two PNFs as well. ‡≤40 years old.

lower graft and patient survival has been less debating [33–41]. It is observed that fibrosis is more rapid and cirrhosis is more common in recipients with HCV who receive organs from older donors [33]; donor age ≥60 years has even been proposed as a major contributor to the recent inferior outcome among HCV positive recipients compared to other recipient categories [34]. Moreover, grafts from older HCV positive donors have been reported to cause significantly more advanced fibrosis compared to HCV positive grafts from younger donors [35]. Proposed mechanisms include accelerated decrease of hepatocyte lifespan in viral hepatitis due to hepatocyte telomere shortening [42]. In animal models, the aging liver has been shown to accumulate mitochondrial deletions, thus leading to an inability to cope with the production of reactive oxygen species (ROS) that enhances apoptosis and subsequent fibrosis [43].

Based on the present data, one may find the following as 'guidelines for elderly donor selection' in the literature. These guidelines, however, are sometimes subjective, not universally accepted, or even contradictory and therefore do not allow drawing precise and uniform evidence-based conclusions. These include careful graft selection (that may result in higher percentage of donor livers discarded), including careful donor medical history, blood tests,

a thorough examination of internal organs during harvesting, and histological evaluation of any suspicious mass, and liberal use of liver biopsy to rule out massive steatosis and HCV-related cirrhosis [20] (which contradicts efforts to keep cold ischemia time low). Cold ischemic time should be kept to a minimum [44–46], ideally less than 6 hours [30] through enhanced coordination (such as starting the recipient operation as soon as possible after verification with the harvesting team [47]). Recipients with hepatitis C should not, when feasible, receive grafts from very old donors [20]; although the cut-off age is not clear and includes a range from <60 to 80 years of age (Table.1). If HCV positive recipients receive grafts from older donors, antiviral therapy should be instituted early after liver transplantation [34]. Some investigators recommend matching the graft to the recipient (i.e., marginal grafts for low-risk patients as opposed to replacement in high-risk recipients—e.g., fulminant hepatic failure—) [48].

Steatosis

Steatosis is increasing in the developed world population and is commonly seen in conjunction with obesity, alcohol use, increased age, and the presence of type 2 diabetes mellitus [49]. There are two histological

patterns of hepatic steatosis: a diffuse small droplet vacuolization (microvesicular steatosis) and a combined pattern of large and small vacuole deposits (macrovesicular steatosis) [50]. The use of grafts with macrovesicular steatosis has been associated with increased rates of initial poor function (IPF), primary nonfunction (PNF), and poorer outcome [51]. Proposed underlying mechanisms include impaired metabolism in the steatotic hepatocytes [52–54], the physical effects of lipid [55,56], particularly during cold ischemia [57], diminished portal blood flow [56, 58], and increased sensitivity to oxidative stress on reperfusion [59–61]. Estimation of steatosis using haematoxylin and eosin (H&E)-stained frozen section liver biopsy has been reported to be difficult and subjective [62,63]. Even Organ Procurement and Transplantation Network (OPTN) data regarding steatosis are recorded in broad ranges and, until recently, did not differentiate between macrovesicular and microvesicular steatosis [8]. Therefore, the reported variability in both the numbers and grading of steatotic donor livers may reflect differences in both qualitative and quantitative evaluations between different centres [64,65]. Some experts believe that physical inspection of an expert in assessing the fat content is equivalent to biopsy [66]; however, this has not yet been validated and remains largely subjective. Body mass index (BMI) per se correlates weakly with presence and severity of steatosis [67]. Imaging studies alone are not proper tools for the accurate quantification of hepatic fat in all donor candidates [68,69]. It has been suggested that differential quantification of colour pixels in Oil Red O (ORO) stained liver biopsies using a computer methodology yields more objective and consistent estimation of liver fat content compared with visual interpretation of H&E stained sections [70], although these computer methods determine the total amount of fat and not the size of the fat droplet (i.e., microvesicular vs. macrovesicular steatosis).

Steatotic livers have been reported to be more susceptible to cold ischemia injury [71,72] and moderate to severe macrovesicular steatosis has been observed as the leading cause of severe liver preservation injury [73]. In one experience with macrovesicular steatotic livers, every additional hour of total ischemia time longer than 10 hours significantly increased the relative risk of graft and patient loss [74]. This highlights the difficult issue of acceptance steatotic livers previously evaluated and refused by other centres, as in these cases ischemia times are always very much longer. Similarly, the additional negative influence of older donor age and hepatic steatosis has been underlined [75]. A large retrospective single-centre study has suggested that recurrent hepatitis C is more common in recipients of moderate and severe steatotic donor livers [76].

Currently, a macrovesicular fat content of 30% in liver graft, a value with a historical basis resting on early nineties' observations, is widely accepted for transplantation [77]. Grafts with moderate

macrovesicular steatosis (30–60%) may be utilized in the absence of additional risk factors in the donor or recipient; livers with more than 60% macrosteatosis should probably be excluded [78]. There are recommendations to allocate livers of different degrees of steatosis based on the Model for End-Stage Liver Disease (MELD) scores of the candidates; these recommendations are however yet to be verified by multivariate analysis [73]. PGE1 has been suggested to be of potential benefit to early allograft function in a steatotic donor liver transplantation model in rats [79]. Only few data is currently available on PGE1 use in human recipients.

Hepatitis C

A mid-1990s review of UNOS registry regarding the clinical outcome of a large series of HCV⁺ recipients of HCV⁺ liver allografts showed that donor hepatitis C status does not impact on graft or patient survival after liver transplantation for HCV⁺ recipients. Their survival was equivalent, if not better, compared with a control group of HCV⁺ recipients of HCV⁻ livers [80]. Data from other large centres have yielded similar results [81,82]. The time to recurrence and the course of HCV disease as well as vector of means of alanine aminotransferase and total bilirubin parallel that in patients who received noninfected organs in a matched-pair analysis over a 3-year follow-up [83], although protocol biopsies were not performed and no data regarding fibrosis scores and virological parameters was available. However, recipients of HCV⁺ grafts from older donors have higher rates of death and graft failure, and develop more extensive fibrosis than HCV⁻ graft recipients from older donors [35]. Finally, the indiscriminate use of HCV⁺ grafts, which constitute approximately 2% to 5% of potential organ pool [84,85], is not recommended as the use of grafts with bridging fibrosis or cirrhosis are unlikely to confer any advantages to a recipient [83].

Hepatitis B

Two to 15% of liver donors are anti-HBc positive. The proportion of positive anti-HBc livers in donors >60 years may rise to 25% [86]. The transmission rate of HBV infection to HBV-negative recipients through this route has been reported to be 17–94% without prophylaxis [87–95]. The use of hepatitis B immune globulin (HBIG), with or without lamivudine, is now used to prevent recurrence of HBV in the recipient as well as transmission from donor to recipient in cases of donor anti-HBc positivity [96]. The 5-year patient and graft survival rate in recipients of anti-HBc positive livers who received dual HBV prophylaxis with HBIG and lamivudine has been reported to be significantly higher than for patients who received single prophylaxis or no prophylaxis [83]. Anti-HBc positive donor livers must be directed selectively first to HBsAg positive recipients – as they will require

life-long HBIG anyway. Secondly, these livers should be directed to anti-HBs positive patients—as they do not seem to require HBIG. It is not clear whether or not to treat anti-HBs negative, anti-HBc positive patients with HBIG. Finally, HBV-negative recipients should only receive these livers in case of critical conditions. Life-long HBIG is mandatory [97]. Given the very costly immunoprophylaxis therapy, there are recommendations for the use of such donors in order to obtain the most justified economic approach. In view of this, serology has been declared to be an insufficient tool to guide the therapy, and determination of donor HBV-DNA status is suggested mandatory at the time of transplantation to allow safe and efficacious use of anti-HBc positive livers. Combined HBIG and lamivudine prophylactic therapy is thus recommended when, at least, donor or recipient is HBV-DNA positive. Lamivudine therapy alone is recommended when donor and recipient are both HBV-DNA negative. If the recipient is HBsAg negative but anti-HBs positive, no prophylaxis is recommended. When HBV-DNA is not available, lamivudine is administered when the recipient is HBsAg and anti-HBs negative [98]. However, if no virological testing is available, long-term immunoprophylaxis is necessary to avoid *de novo* infection [98].

Intensive care unit (ICU) stay and bacteraemia

Donors with a prolonged ICU stay are at increased risk of infection. A multivariate analysis of the results of microbiologic cultures obtained before and at harvesting from 610 consecutive liver donors has shown an ICU stay of ≥ 3 days to be the only significant donor characteristic to predict donor infection [99]. Therefore, adequate donor maintenance and careful microbiologic surveillance and treatment, especially of elderly donors, may limit transmission of donor infection. Most of the larger series investigating the bacteraemic donors suggest that livers procured from bacteraemic donors are likely to function well and pose little if any increased risk to the recipient, provided that the recipient is treated with antibacterial agents active against the donor bacterial isolate [100–103]. However, there is no controlled trial indicating the optimal duration of antibacterial treatment for recipients of organs from bacteraemic donors. Five to 7 days of appropriate therapy seems to be the most frequently cited regime [104].

Malignancy

A survey of UNOS Tumour Registry data has demonstrated extremely low rates of donor cancer transmission through organ transplantation. Among 31986 liver transplants from 1994 through 2001, there are only 7 cases of tumour transmissions (0.02%), although with a high mortality of 57% [105]. There has been a consensus that melanoma, choriocarcinoma, and lung cancer are associated with extremely high

transmission rate and subsequent mortality and therefore should be considered absolute contraindications to organ donation [105]. Data on central nervous system (CNS) tumours has been debating [106–108]. Current consensus is that certain histologic types of CNS tumours such as glioblastoma multiforme and medulloblastoma, along with clinical history of ventricular shunting, major craniotomy, and/or extensive radiation increase the risk of transmission [105].

Ischemia

Cold and warm ischemia times have been identified as independent risk factors for mortality; they should be minimized to also mitigate unfavourable donor characteristics. An ELTR analysis of 34664 primary adult liver transplants has identified a total ischemia time > 13 hours to be associated with significantly increased mortality at 3- and 12-months post-transplantation [4]. As a previous ELTR analysis had identified a cut-off of 12 hours [109], the current recommendation is to try to keep total ischemia time below 12 hours although the precise threshold for improved outcome is unclear [4]. Programs using significant numbers of EDC livers should consider using the piggyback technique for all cases to minimize warm ischemia time [10,96,110]. Organ procurement and/or allocation from non-heart-beating donors (NHBD) is prohibited according to the German law on transplantation [111].

Conclusion

Systematic liberalization of graft acceptance criteria provides an immediate expansion of the donor pool with acceptable graft and patient survival. However, risk factors for poor outcome should be identified and avoided in order to avoid “futile transplants”. There is no age limit to be an organ donor. However, recipients with hepatitis C should not, when feasible, receive grafts from very old donors. Grafts with moderate macrovesicular steatosis (30–60%) may be utilized in the absence of additional risk factors in the donor or recipient; livers with more than 60% macrosteatosis should probably be excluded. Donor hepatitis C virus (HCV) status does not impact on graft or patient survival after liver transplantation for HCV+ recipients. The use of hepatitis B virus (HBV) immune globulin (HBIG), with or without lamivudine, is used to prevent HBV transmission from donor to recipient in cases of donor anti-HBc positivity. Adequate donor maintenance and careful microbiologic surveillance and treatment of donors with a prolonged ICU stay is necessary. History of melanoma, choriocarcinoma, and lung cancer precludes organ donation. History of glioblastoma multiforme and medulloblastoma in donors also increase the risk of transmission to the recipient. In order to optimize effective utilization of EDC, a careful consideration of recipient outcome with these organs and a careful matching of the most

appropriate graft-recipient pair should be made while trying to keep cold and warm ischemia times as short as possible and prompting to perform a retransplantation when necessary.

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