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University of Muenster and university of Heidelberg, 2018

Is there an ethical obligation to split every donor liver? Scarce resources, medical factors, and ethical reasoning

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Abstract

Split liver transplantation (SLT) has the potential to counter the worldwide shortage of donor organs. Although the preferred recipients of SLT are usually pediatric patients, a more stringent ethical argument than the fundamental prioritization of children is to demonstrate that SLT of deceased donor organs could increase access to this potentially life-saving resource for all patients, including children. Several empirical studies show that SLT also makes it possible to achieve similar outcomes to whole liver transplantation (WLT) in adults if several factors are observed. In general, it can be regarded as ethically permissible to insist on splitting a donor liver if, in an individual case, SLT is expected to have a similar outcome to that of WLT. The question is therefore no longer whether, but under what conditions SLT is able to achieve similar results to WLT. One of the main challenges of the current debate is the restricted comparability of the available data. We therefore have an ethical obligation to improve the available empirical data by implementing prospective clinical studies, SLT programs, and national registries. The introduction of two modes of allocation – one for patients willing to accept both SLT and WLT, and a second for patients only willing to accept WLT – would help to resolve the issue of patient autonomy in the case of mandatory splitting policy.

Keywords

Split liver transplantation, mandatory splitting policy, ethics, deceased donor organ allocation, prioritization of children, patient autonomy.

Abbreviations

BMI = body mass index

GRWR = graft-to-recipient weight ratio

ICU = intensive care unit

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SFSS = small-for-size syndrome

SLT = split liver transplantation

WLT = whole liver transplantation

1. Introduction

Various strategies have been discussed to counter the worldwide shortage of donor organs. Split liver transplantation (SLT) could increase the efficiency of liver allocation, as it allows allocation of a single deceased donor liver to several recipients instead of just one.⁵ In practice, the preferred recipients of SLT are pediatric patients – not just because there is only a very limited number of whole grafts available for small children, such that pediatric patients largely rely on SLT, but also because splitting a liver between two adults still raises the concern of a poor outcome. The split graft might subsequently be lost due to complications associated with the complex surgical intervention and small-for-size syndrome (SFSS). It is also believed that the potentially negative outcomes of SLT could further increase the shortage of donor organs. Split grafts have traditionally been considered high-risk.^[1,2]

In contrast, several studies show that SLT now has the potential to achieve outcomes similar to those of whole liver transplantation (WLT) if several factors are taken thoroughly into account.^[3,4,5,6] The question is therefore no longer whether, but under what conditions SLT is able to achieve results similar to those of WLT.^[7] The aim of this contribution is to critically assess, from an ethical point of view, the main criteria that are discussed in studies comparing the outcomes of SLT and WLT in adults.

On the basis of these empirical findings, we will explore whether a mandatory splitting policy can be defended from an ethical point of view. Prioritization of children for liver allocation is practiced in several countries and various ethical arguments have been offered to justify this practice.^[8,9] One ethical concern that remains unresolved is the argument that fundamental prioritization of children denies adult patients an equal right to the potentially life-saving treatment of liver transplantation. A more promising ethical strategy is to demonstrate that SLT could increase access to this potentially life-saving resource for all patients, including children.

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In order to acquire empirical proof for such a normative claim, it is necessary to prove that SLT is also a viable option for adult patients. As it is pediatric patients that largely or even exclusively rely on SLT,^[9] the question of whether it is ethically permissible to impose a mandatory splitting policy for adult patients also opens up the opportunity to increase the number of split grafts available to the pediatric group.

2. Methods

PubMed and Livivo were used as electronic databases to retrieve studies and reviews that directly compare the outcome of SLT and WLT in adults. Publications confined to living donation were excluded from the analysis. A critical synopsis of the current state of the debate on the comparability of the outcome of SLT and WLT was elaborated. The most relevant factors believed to influence the outcome – especially factors in the selection of appropriate donors and recipients of liver splits – were identified. The research focused on factors to form the basis of future SLT programs and prospective studies on the outcome of SLT. Another step was to identify and apply to the empirical findings the main ethical approaches that dominate the ethical debate on the allocation of deceased donor organs. These are presented in section 4, together with an elaboration of the question of whether it is ethically permissible to split any donor liver that is deemed suitable for SLT.

3. Results: Comparability of outcomes of SLT and WLT

One of the main challenges of the current debate on the outcome of SLT in adult patients is the restricted comparability of the available data. The outcomes of SLT and WLT are difficult to compare because there is no internationally recognized standard protocol that could be universally implemented in clinical studies and SLT programs.^[10] SLT is subject to a number of variations that may significantly influence its outcome.^[11] Not all studies provide sufficient information on the surgical procedures or the donors and recipients of SLT, or the organizational structures and experience of the surgical team. From an ethical point of view, the implementation of standardized national transplantation registries is highly recommended. This would enable the collection of this much-needed information for reliable comparison and, later, prediction of the outcomes of SLT and WLT. Although there appears to be a consensus that the criteria for SLT should be stricter than for WLT, it is not currently possible to draw any definite conclusions concerning the criteria that should be implemented in SLT. Instead, we

have identified the main criteria for further consideration in future studies and the establishment of national registries.

3.1. Medical factors concerning donors

There is a broad consensus that age is a relevant clinical factor in selecting donors for SLT.^[12] Some authors claim that donors should be under 50 years of age.^[13,14] Others view this age group as too risky^[15] and recommend that the donor age should be between 10 and 40 years.^[16,17,18] It has been suggested that weight, hemodynamic stability and liver enzyme level are more reliable criteria than age, and that pediatric liver transplantations from older donors (\geq 50 years) also show satisfying long-term outcomes.^[19] The growing number of older donors makes donor criteria that include this group of donors as possible candidates for SLT more attractive.^[16]

Body weight is discussed as a relevant factor with particular reference to steatosis and its potentially negative effect on the outcome of SLT. Some clinical studies recommend restrictions on donors with a body mass index (BMI) of 30 kg/m².^[17] Others prefer steatosis as a criterion for exclusion,^[15,14] as the condition is believed to be associated with a decrease in positive outcomes.^[20] However, it has been suggested elsewhere that the degree of steatosis is a poor predictor of outcome.^[18]

Infections and malignancies, especially malignant neoplasms with metastases or those of hepatic origin, are reasonable factors for exclusion.^[15] Several studies include medication in their donor criteria in order to reduce the risk of hemorrhaging. Studies suggest maximum of one antihypertensive drug^[17] and hemodynamic stability^[15]. They also suggest that hospitalization should be less than 7 days^[17] and treatment in the intensive care unit (ICU) less than 5 days.^[14]

3.2. Medical factors concerning recipients

As SLT can be related to additional complications and a longer recovery time,^[15] special attention needs to be given to informed consent. The patient (or their relatives) should receive a detailed verbal explanation of the risks and benefits of SLT in comparison to WLT. They should be made aware that there are still no internationally recognized standard protocols for SLT. They should also be provided with information on the experience of the surgical team in

SLT. It should be made clear that the patient is free to refuse SLT at any time and that refusal will not have any negative impact on their relationship to the healthcare team.

One factor that has a major impact on the outcome of SLT is the graft-to-recipient weight ratio (GRWR).^[15] To meet the functional demands and minimize the risk of graft loss, the graft must be of an adequate size. A minimum GRWR of 0.8/100 is commonly recommended.^[21] Some studies favor a correlation of ≥ 1 percent in the case of SLT.^[20,22] It may also be important to match liver volumes in order to avoid large-for-size syndrome, which could lead to graft loss due to insufficient blood supply.^[23]

The recipient's general state of health must also be considered. Unsurprisingly, the outcome of liver transplantation tends to be better if recipients are still in a good state of health.^[12] This has led many studies to exclude high-urgency or re-transplant patients from SLT. Such patients are usually admitted to ICU prior to transplantation, which increases the risk of complications and a worse outcome of SLT.^[6] However, some studies report similar outcomes for SLT and WLT in both high urgency and re-transplantation patients, as well as for recipients with a high MELD score.^[24] This suggests that further analysis of the outcome of SLT in these patients is necessary. Some studies also suggest that information on previous abdominal operations should also be included in prospective studies and registries.^[3]

Other factors that may affect outcome include the various disorders that lead to an indication for liver transplantation. A retrospective study demonstrated that patients with primary sclerotic cholangitis had better 1- and 3-year survival rates than patients with other indications.^[25] We therefore suggest that the different medical conditions leading to the need of transplantation should be included in further studies and registries, along with the other recipient criteria mentioned.

3.3. Organizational factors and factors concerning the transplantation center

As mentioned above, SLT is subject to a number of variations that are likely to affect the outcome of transplantations. SLT can be performed by splitting the liver in-situ or ex-situ. The in-situ technique reduces the risk of bleeding and graft damage, as it offers the surgeon better orientation and an improved view of the anatomical structures of the graft. Cold ischemia time, which is a common objection against an increase in SLT treatments, is reduced.^[26] Furthermore, the different splits can be easily transferred to separate transplantation centers.^[27,28] In contrast,

the ex-situ technique has the advantage that it can also be applied to less hemodynamically stable patients, and that the splitting of the graft can be performed by surgeons in the implanting center.^[29]

The outcome of SLT also depends on the type of split graft. In one study, recipients of left lateral splits (segments 2 and 3) had better outcomes than patients who had received right-extended lobes (segments 1, and 4-8) or full-right (segments 5-8) or full-left splits (segments 1-4).^[27] A retrospective study that compared WLT to the transplantation of right-extended lobes showed similar survival rates, although the latter were linked to a higher risk for retransplantation.^[1,30] In contrast, recipients of full-left splits showed more complications in a study that compared full-left and full-right SLT.^[17]

The outcome of complex surgical interventions largely depends on surgical precision and the training of the attending surgeons – a correlation that also applies to the outcome of SLT.^[31,27] A cross-center study suggests that a significant improvement in outcome is achieved as soon as the surgical team has carried out around 30-50 SLTs.^[32]

SLT has greater logistic and financial costs than WLT (e.g. a third surgical team is needed). A lack of sufficiently trained surgical teams or logistical deficiencies can have negative impacts on the outcome of SLT or provoke the loss of the second split.^[33,27] The cooperation between explanting and implanting centers varies considerably on an international level.

The factors that are believed to influence the outcome of SLT (e.g. the underlying diseases) may vary considerably between pediatric and adult patients. It is not possible to comment on these differences here, but they should be given appropriate consideration in prospective studies. Particular consideration should be given to differences in short- and long-term complications after transplantation in children (e.g. age at time of diagnosis, growth retardations, developmental deficits in children, transitional healthcare, long-term outcome).

4. Ethical Discussion

SLT has been discussed for decades as a viable strategy to alleviate the worldwide scarcity of donor organs.^[36,37,38,39] It has been estimated that in the USA, 20 – 28% of deceased donor livers

could be used for SLT. In 2016, only 1.2% of adult liver transplant recipients received SLT in the US, compared to 14.4 % of pediatric liver transplant recipients.^[40 (pp. 72,82)] In 2017, 74 out of 686 deceased liver transplantations were SLTs in Germany.^[41 (p. 32)] Children in particular could profit from an increase in SLT, as very few whole grafts are available for them. Specific split liver programs, for example in Northern Italy, have shown that a split liver rate of more than 20% can be achieved.^[27] Following these positive results, Italy has opted for a national policy that demands that every liver from adult donors aged ≥ 50 years is to be evaluated for SLT.^[30]

The information above might give rise to question why it is not the case that every liver deemed suitable for SLT is split, at least as long as children are waiting for a donor liver. Prioritization of children is commonly used to justify SLT as very few whole grafts are available for them.^[9] The section below will discuss the main arguments and main criticisms offered for prioritizing children for organ allocation. In the second part of the section an alternative strategy will be developed to justify a mandatory splitting policy that avoids the major shortcomings of the arguments that rely on fundamental prioritization of children. Some general ethical prerequisites for the implementation of a mandatory splitting policy will also be outlined.

4.1. Prioritization of children – the argument for and unresolved issues

The ethics of deceased donor organ allocation usually revolves around the question of how to balance different allocation criteria against one another. Particularly important aspects include utility (e.g. efficiency), urgency (i.e. need) of transplantation, and the concern for fairness, i.e. the belief that every patient should be given equal access to the scarce resource of donor organs. These aspects can be weighed and interpreted differently depending on the ethical approach one takes. As will be shown, prioritization of children has been both justified and challenged with reference to all three aspects (i.e. utility, urgency and fairness).

Utility

In general, elderly and adult patients are more likely to die with a graft that is still functioning than pediatric patients. This is true to such an extent that favoring children has the potential to maximize the number of life years gained from the available pool of deceased donor organs.^[42 (p.335)] Fundamental prioritization of pediatric patients is therefore often justified with reference to the criterion of utility.^[8] However, in addition to the issue that utility is just one of the aspects

that should be taken into account in liver allocation, doubt has been expressed as to whether general prioritization of children really represents the best strategy to maximize utility.

First, some adult patients, especially those between 20 and 40 years of age, may live just as long with a functioning graft as pediatric patients.^[42(p.335)] Furthermore, it is argued that adolescence is a critical period linked to an increase of non-compliant behavior and complications in transplant recipients,^[43,44,45] just as quite a few adults show non-compliant behavior after transplantation. It has therefore been maintained that the aspect of utility calls instead for further empirical differentiation to identify those subgroups in pediatric and adult patients that show the best outcome, instead of prioritizing all children.^[46] Second, it has been argued that fundamental prioritization of children may lead to a decrease in living donations for the pediatric group and that the shortage of organs within the deceased donor allocation might even rise, which would jeopardize the aim of maximizing the overall utility of organ allocation.^[42 (p.33), 46 (p.537 f.)]

Urgency

Pediatric priority programs are also defended with reference to the urgency of transplantation and the need of the patients. Urgency in the case of adult patients is predominantly interpreted as risk of mortality. However, pediatric patients are exposed to additional risks, namely the risk of irreversible growth and neurological, cognitive, or social developmental deficits.^[46 (pp. 534 f), 47,48] As these risks represent a special form of urgency and need, they could justify a prioritization of pediatric patients to prevent these forms of impairments.^[8]

However, this line of argument presupposes that the risk of developmental deficits in children should be regarded as ethically more important than the risk of mortality of adult patients. This is hard to defend, as in the latter case patients are about to lose everything they have, namely their lives.^[49(p.89)] The aspect of urgency instead calls for a mode of allocation that prioritizes pediatric and adult patients primarily according to their risk of mortality. The claim that developmental deficits in children should be given a higher priority can only be justified with reference to considerations of fairness, which will be discussed next.

Fairness of organ allocation

One argument for maintaining that children suffering from end-stage liver disease are worse off than adult patients is that equity and justice requires an “over-a-lifetime-perspective”.^[42 (p.338)]

According to this view, children should be regarded as worst off, as they do not have the opportunity to grow old and experience the various stages of human life.^[42 (pp.338 f.),46 (p.534)] This is sometimes called the “fair innings argument”, as otherwise, the pediatric patients would not have “a fair share of life”.^[49 (p.91)]

Proponents of this argument^[8] overlook that the concept of a “fair innings”, which goes back to John Harris^[49], does not justify fundamental prioritization of children. It only excludes those patients that have already achieved a “fair innings”, i.e., a stage that can be considered a “reasonable life”.^[49(p.91)] Whatever we regard as a reasonable lifetime (Harris suggests a time span of 70 years) all patients that are not able to reach the threshold suffer the same injustice. If a patient is excluded at the age of 50 from a lifesaving resource, he or she has not had a greater or more equal chance to reach the threshold than if he or she had been excluded at the age of 40 or 30 years.^[49 (p.91)] According to this objection, general prioritization of pediatric patients represents discrimination against persons on the basis of age, sometimes called ageism. The argument continues that although patients can legitimately be excluded from organ allocation if they have reached the as yet to be defined threshold of a reasonable lifetime, the concept of a “fair innings” does not regard every age difference as morally significant, such that a child could be prioritized over a 30 or 40 years old patient purely on the basis of their relative age.

A similar line of argumentation has been offered by Norman Daniels’ “prudential lifespan account”.^[50] Daniels argues that any rational person would prefer to allocate healthcare resources in such a way that they maximize the chance of every individual to live through childhood and adolescence and to reach a reasonable, normal lifespan. He invites us to think of the allocation of health resources not as a competition between different groups (e.g. the young and the elderly), but rather as an allocation over the different stages of a human life.^[50 (pp. 171 ff.)] Although the concept of a “prudential lifespan account” has subsequently been used to justify fundamental prioritization of children for organ allocation,^[8] Daniels does not believe that his own account offers straightforward support for such a policy.^[50 (pp. 175 f.)] In his opinion, he argues against the use of scarce, expensive healthcare resources (e.g. dialysis and transplant surgeries) to merely provide a small extension of life, especially in elderly people, who have already reached a normal and reasonable lifespan.^[50 (pp.178 ff.)]

Just as in the case of the concept of a “fair innings”, the aim of the “prudential lifespan account” is to maximize every individual’s chance to reach a normal lifespan. In addition to the fact that the “prudential lifespan account” only offers a very narrow view of what a fair and reasonable allocation of healthcare resources should look like, it only provides a firm basis for excluding patients that have already reached a normal and reasonable lifespan. It does not provide a firm basis for prioritization of children over young adult and middle-aged patients.

As the brief analysis above shows, several strategies have been offered to justify fundamental prioritization of children. All of them have been criticized for various reasons. Whatever side one takes, a more promising strategy consists in demonstrating that SLT has the potential to increase the chance of every single patient to obtain access to this potentially lifesaving resource. As mentioned in the opening section, several studies have shown that SLT is also able to achieve results similar to those of WLT in adults. This article argues that a mandatory splitting policy has under certain circumstances the potential to increase every single individual’s chance of obtaining access to the potentially lifesaving resource of liver transplantation and that, it can therefore be regarded not only as ethically permissible but also as an ethical obligation to split every donor liver that is deemed suitable for SLT.

4.2. Maximizing overall utility

A mandatory splitting policy can be easily defended from an ethical perspective that stresses the aspect of utility, as it has the potential to maximize overall utility. In contrast, mandatory splitting policies are much harder to reconcile with the aspect of urgency and the concern for fairness, both of which emphasize the individual patient’s equal right to the potentially lifesaving resource.

Nevertheless, it is possible to reconcile a mandatory splitting policy with the criteria of urgency and fairness of liver allocation under the following conditions: If the outcome of SLT in an individual patient is deemed to be as good as for WLT, the patient has no ethical right to insist on undergoing WLT. In this case, no patient has the right to claim a greater share of a scarce potentially lifesaving resource if his survival and well-being can be readily secured with a smaller share, such that the remaining part can be used to save the life or secure the well-being of another patient. In contrast, if a patient does not fully meet the recipient criteria for a successful SLT, such that a worse outcome is expected than with WLT, it would amount to a

disrespect of his fundamental right to assistance if he were forced to accept SLT. The individual's unalienable right to a potentially lifesaving resource cannot be disregarded simply because an alternative allocation of the scarce resource yields a greater overall utility.

Splitting every liver that is deemed suitable for SLT, not only maximizes overall utility, it also maximizes every patient's chance of receiving a donor liver since expanding SLT makes it possible to allocate a single transplant to more – not exclusively pediatric – patients. As more patients can undergo transplantation in the same time span, every single patient has a higher chance of access to a potentially lifesaving graft. This also applies to those patients who because of their condition are certain to require a whole graft to achieve an acceptable outcome. Under these circumstances, it should be regarded as an ethical obligation to increase the efficiency of deceased liver allocation by splitting every liver that is deemed suitable for SLT.

4.3. Respecting patient autonomy under a mandatory splitting policy

In several transplantation centers that follow an optional splitting policy, it is common practice to inform patients of the opportunities presented by WLT and SLT, and to give them the option of consenting to one or both of these surgical procedures.

To respect the autonomy of patients in the case of a mandatory liver splitting policy, the introduction of a special mode of allocation should be envisaged for patients who are willing to accept both WLT and SLT, as long as they meet the relevant requirements for successful SLT (allocation mode for SLT). In such cases, patients that insist on undergoing WLT should be made aware of the fact that every donor liver that is deemed suitable for SLT will be mandatorily offered to patients who have consented to SLT, such that patients who have consented only to WLT will eventually face a longer waiting time. These two modes of allocation should also be used in prospective studies on SLT and the implementation of SLT programs.

4.4. Maintaining national allocation criteria

On a national basis, the same allocation criteria as before could be applied, i.e., every national organization could decide on its own how much weight they want to give to the aspects of urgency and prospects of outcome in their centralized allocation decisions. Rather than

prioritizing children absolutely, pediatric and adult patients should be equally ranked according to urgency and prospects of outcome. Under such a policy, a child would still be preferred to an adult patient if his or her urgency were higher or/and prospects of outcome were better.

The various allocation guidelines could easily be supplemented by organizational criteria as well as donor and recipient criteria to evaluate the suitability of grafts and potential recipients for SLT. In this case SLT should be performed every time a specific pediatric or adult patient and the available graft are deemed suitable for splitting. The second split could simply be allocated to the next suitable pediatric or adult patient on the waiting list, or preferably to pediatric patients. The latter would amount to a relative prioritization of pediatric patients, which can be more easily defended from an ethical point of view than an absolute prioritization of children. Such a relative priority policy would still allow a considerable reduction of the pediatric waiting list, without imposing any morally significant burden on adult patients. It could be used as a supplement to the aforementioned “regular” allocation of liver splits to children based on the criteria of urgency and prospects of outcome, as children in general (and especially those in the weight range 30-40 kg) are in special need of a split liver because size-matched whole organs are rarely available.

4.5. Ethical rules for institutions of healthcare

It is a well-known problem that the cooperation between explanting and implanting centers varies considerably on an international level. Nevertheless, the explanting surgeon has an ethical responsibility to ensure and maximize the outcome for both splits, irrespective of whether both or none of the splits will be allocated to one of his own patients.

Some have argued that the transplantation centers should be given the right to allocate the second split themselves.^[51,10] This is seen as a possible incentive for transplantation centers to increase the number of SLTs.^[52,32] However, a centralized allocation system is in a better position to guarantee the equal treatment of all the patients on the waiting list. Furthermore, it avoids the ethically challenging situation in which a physician has to decide which of his patients should be given the right to a potentially lifesaving resource and which should be denied such an opportunity.

5. Ethical conclusions

We have argued that the medical and ethical question is no longer whether, but under what conditions SLT is able to achieve results similar to those of WLT. More SLTs would save more lives and therefore children and adults would benefit equally from this technique. As SLT has the potential to increase every individual patient's chance of obtaining access to the potentially lifesaving treatment of liver transplantation, we argued in favor of an ethical obligation to improve the available empirical data on SLT. This can be done through the implementation of prospective clinical studies, SLT programs, and national transplantation registries. These should include at the very least the above-mentioned factors concerning the donors⁶ and recipients⁷ of liver splits, as well as relevant information on surgical procedures⁸, the experience of surgical teams, and the outcome of the different liver splits. The additional data would improve the comparability of the outcome of SLT and WLT for different constellations of donors and recipients and provide evidence as a basis for the decision on whether or not to split a given donor liver. This could in future lead to the development of a split score to help decide which donor livers should be mandatorily split and to institutionalize SLT. Although the implementation of prospective clinical studies and SLT programs may seem challenging, previous examples have shown that it is feasible.^[22]

If the outcome of SLT in an individual case is deemed to be as good as for WLT, it can be regarded as an ethical obligation to insist on splitting a given donor liver. As long as the factors that determine the outcome of SLT remain the object of clinical research, two modes of allocation – one for patients willing to accept both WLT and SLT, and one for patients insisting on WLT – should be introduced to satisfy the individual's right to autonomy. No patient has the right to claim a greater share of a scarce potentially lifesaving resource if his survival and well-being can be readily secured with a smaller share, such that the remaining part can be used to save the life or secure the well-being of another patient.

6 Data should include at the very least information on age, BMI, degree of steatosis, hemodynamic stability, liver enzyme level, medication, hospitalization and ICU care.

7 Data should include at the very least information on GRWR, MELD score and general state of health, high-urgency or re-transplant status, hospitalization and ICU care, abdominal operations, and underlying diseases. In the case of pediatric patients it should also include information on age at the time of diagnosis, any growth retardations, developmental deficits, transitional healthcare, long-term outcome, etc.

8 Mandatory categories should be in-situ, ex-situ, left-lateral, right-extended, full-right, and left-split.

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