CON: Patients of Advanced Age Should Not Routinely Undergo Liver Transplantation

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KEY POINTS

- Careful patient selection forms the foundation for improving patient outcomes after liver transplantation (LT). This also provides inherent selection bias in studies suggesting comparable post-LT outcomes in patients with advanced age compared with younger cohorts.
- Despite this, studies from the United States, Europe, and Asia have demonstrated higher mortality in transplant recipients of advanced age.
- Older transplant recipients in the United States are more likely to receive grafts from older donors. The use of organs from older donors (>60 years old) is associated with worse 5-year graft outcomes and increased 5-year mortality, further compounding the increased mortality in transplant recipients of advanced age.
- Studies supporting the “pro” argument have significant limitations that preclude generalizability for most transplant centers.

In the United States, the number of individuals older than 75 years is projected to double to more than 10% of the population by the year 2050,¹ and the question of whether to transplant patients of advanced age has thus become increasingly relevant. In practice, however, this is not a question of whether these patients deserve transplantation any more or less than younger patients. Nor is it a question of whether the transplant community is capable of successfully transplanting and caring for such a patient.

After all, in the modern era of LT, overall 5-year graft and patient survival are each greater than 70% and continue to improve.² Although this is a testament to high-quality medical and surgical care of transplant registrants and recipients, the foundation for these outcomes is responsible allocation of donor organs via careful patient selection for transplantation. In that context, patients of advanced age (>70 years) should not routinely be considered appropriate candidates for LT.

Abbreviations: LT, liver transplantation; MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing. From the Division of Gastroenterology and Hepatology, University of Colorado School of Medicine, Aurora, CO.

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DONOR ORGANS ARE A SCARCE RESOURCE

Clinicians caring for patients awaiting LT must be responsible stewards of a scarce resource. The number of patients awaiting a donor liver greatly exceeds the number of available grafts. More than 6000 liver transplants are performed annually in the United States, but there are more than 15,000 patients awaiting LT. Furthermore, in 2016, 2600 patients died while on the LT waiting list or were removed for becoming too sick to undergo a transplant.^{2,3}

These data underscore the critical importance of patient selection. Since the implementation of the Model for End-Stage Liver Disease (MELD) score in 2002, clinicians have enhanced their ability to better predict both wait-list mortality and posttransplant outcomes, with emerging data over the past two decades examining the impact of hyponatremia, frailty, body mass index, cardiovascular disease, graft selection, geographic sharing, and yes, age.⁴⁻¹⁰

ADVANCED AGE IS ASSOCIATED WITH INCREASED POST-LT MORTALITY

According to the most recent national data provided by United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network on posttransplant outcomes, patients older than 65 years have worse graft (Table 1) and overall survival at 1, 3, and 5 years post-transplant compared with younger cohorts.¹¹ For recipients older than 65 years, the unadjusted 5-year graft survival rate is 65.9%, the worst outcome of any age group.

Data show that advanced age is a risk factor for poor outcomes. Sharpton et al.¹² (Fig. 1) demonstrated that age older than 70 years is a risk factor for graft loss and mortality, particularly among those with physiological MELD greater than 28, with a 1-year graft survival rate of only 56%. The risk appears universal, with higher mortality in transplant recipients of advanced age in studies using both the UNOS database and the European Liver Transplant Registry.^{13,14}

TABLE 1. LOWER UNADJUSTED SURVIVAL RATES IN LT RECIPIENTS OLDER THAN 65 YEARS³

Follow-up Time	Unadjusted Survival Rates in LT Recipients			
	Age 18-34 Years	Age 35-49 Years	Age 50-64 Years	Age ≥ 65 Years
1 year	90.9%	90.1%	89.1%	86.6%
3 years	81.3%	82.1%	79.8%	75.2%
5 years	72.7%	75.0%	71.0%	65.9%

Number at Risk				
Age 18-59	4235	3415	2845	2105
Age 60-64	630	466	391	275
Age 65-69	324	231	198	138
Age ≥70	76	42	32	21

FIG 1 Graft survival in recipients with MELD greater than 28 by LT age categories. (Reprinted with permission from *Transplantation*.¹² Copyright 2014, Wolters Kluwer Health, Inc.)

In addition, a recent Korean cohort study of 9415 liver transplant recipients found that, when compared with patients aged 51 to 55 years, the risk for in-hospital mortality among recipients older than 70 years was approximately 4-fold higher.¹⁵ After adjusting for baseline liver disease and perioperative complications, the risk for death was nearly 3-fold higher. The cost of liver transplant also increased significantly with age, a 9.7% increase in the elderly group. Notably, 74% of the transplant recipients included in the study underwent living donor liver transplants, therefore representing an even more highly selected population than deceased donor transplantation recipients.

The U.S. experience was evaluated with a retrospective cohort study of 35,686 liver transplant recipients aged 50 or older from February 2002 through October 2011.¹⁶ The study authors, from Yale University, found statistically significant lower 5-year survival rates in patients aged 65 to 69 years and patients older than 70, compared with younger cohorts. Moreover, older transplant recipients in the United States are more likely to receive grafts from older donors. The use of organs from older donors (>60) is associated with worse 5-year graft outcomes and is independently associated with increased 5-year mortality after adjusting for other variables.

REBUTTAL TO THE “PRO” ARGUMENT

Using the UNOS database to examine 60,820 liver transplants in the United States from 2002 to 2014, Su et al.¹⁷ concluded that, although increasing age was associated with worse posttransplant outcomes, it does not affect transplant-related survival *benefit*, a novel metric calculated as the difference between wait-list and posttransplant life expectancy, because age diminishes both post-LT survival and wait-list survival equally.

However, survival benefit is not currently considered in allocation policy, and even if it were, the metric is based

on modeling using unproven assumptions regarding wait-list survival. Furthermore, the impact of survival benefit was evaluated for 5 years. It is unknown whether this putative benefit would be sustained over a longer follow-up period, such as at 10 to 15 years, an important variable given the continued improvement in long-term survival of LT recipients.

Several additional studies have suggested that older patients have comparable survival rates with younger cohorts, but these studies have significant limitations.¹⁸⁻²¹ Because UNOS measures center performance as a metric of accountability and because risk is not age adjusted, patients of advanced age transplanted in the current U.S. allocation system are highly selective. Therefore, any study suggesting that patients of advanced age have comparable survival rates with younger cohorts is fraught with selection bias, because any “elderly” patient who is transplanted is carefully selected to minimize risk to the transplant center. This practice is not generalizable to most older patients with multiple medical comorbidities.

Kollman et al.¹⁸ in a single-center study compared 76 patients aged 65 years or older who received LT with 1395 patients younger than 65 years, and suggested comparable 1- and 5-year survival rates for the two age groups. However, LT recipients in the “elderly” group had an average physiological MELD at transplant of 17, and more than half received an organ from a donor younger than 50 years old—practices that are not representative of most centers in the United States. Notably, the authors did demonstrate a significant reduction in postoperative survival in patients older than 65 years with a more extended follow-up beyond 5 years.

Finally, the most compelling pro argument may be a meta-analysis of 22 studies comparing outcomes of “young” LT recipients (n = 218,827) and “elderly” LT recipients (n = 23,660).¹⁹ However, according to the GRADE (Grading of Recommendations Assessment, Development,

TABLE 2. RELEVANT STUDIES EXAMINING AGE AND POST-LT OUTCOMES

Study	Key Findings/Relevance
Sharpton et al. ¹² (<i>Transplantation</i> 2014)	Age >70 years is a risk factor for graft loss and mortality, particularly among those with MELD >28
Schwartz et al. ¹³ (<i>Liver Transplantation</i> 2012)	Higher mortality in transplant recipients of advanced age in analysis of the UNOS database
Burroughs et al. ¹⁴ (<i>Lancet</i> 2006)	Higher mortality in transplant recipients of advanced age in analysis of the European Liver Transplant Registry
Gil et al. ¹⁵ (<i>Transplantation</i> 2018)	Korean cohort study of 9415 LT recipients; when compared with patients aged 51 to 55 years, the risk for in-hospital mortality among recipients >70 years old was approximately 4-fold higher
Malinis et al. ¹⁶ (<i>Annals of Transplantation</i> 2014)	Retrospective cohort study of 35,686 LT recipients aged ≥50 years: statistically significant lower 5-year survival rates in patients aged 65-69 years and patients >70 years compared with younger cohorts; in addition, use of older donors (>60 years) was associated with worse 5-year graft outcomes and increased 5-year mortality

and Evaluation) system of scoring studies, evidence in each of the 22 studies was low quality or very low quality. The definition of “elderly” also conflicted, defined as older than 63 years in one study, older than 65 years in 13 studies, and older than 70 years in 7 studies. Lastly, graft loss was analyzed in only 3 of the 22 studies, and no study defined how graft loss was calculated.

CONCLUSIONS

A carefully selected patient of advanced age without medical comorbidities may be considered an appropriate transplant candidate, although this is most certainly the exception and not the rule. Even then, projecting survival while committing these patients to lifelong immunosuppression is difficult given limited long-term data in this relatively small percentage (2%) of LT recipients.¹²

In order to be a responsible steward of the scarce resource that is available donor grafts, one must remain objective. Simply, the preponderance of data (Table 2) show that patients in their eighth decade of life have poor outcomes after LT; therefore, in general, these patients should not be considered LT candidates.

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