Liver and Kidney Transplantation in Elderly Patients

John Guzzi, Eric Strand, Burhan Ozturk, Daniel Agarkov and Ranjit Deshpande*

Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510, USA; john.guzzi@yale.edu (J.G.); eric.strand@yale.edu (E.S.); burhan.ozturk@yale.edu (B.O.); daniel.agarkov@yale.edu (D.A.)
* Correspondence: ranjit.deshpande@yale.edu

Abstract: Due to an aging population, advances in multiple medical fields, and shifts among indications for surgery, liver and kidney transplantation is increasingly pursued for elderly patients (aged 65 or greater). Elderly patients represent a uniquely vulnerable group, but overall, they appear to have similar outcomes compared to younger patients. As demographics continue to trend to an older median age, physicians and health care systems must be prepared to take care of elderly transplant candidates.

Keywords: transplant surgery; transplants in the elderly; liver transplant; kidney transplant; geriatrics; transplant medicine; solid organ transplantation

1. Introduction

Elderly adults (age 65 years or greater) are the fastest growing segment of the United States population [1]. Currently, 16.5% of the U.S. population is 65 years or older. By 2030, 21% of the U.S. population is projected to be 65 years or older, and this proportion will only continue to grow in the coming decades [2].

With increased age, there is an increased burden of comorbidities and an increased potential for end-stage organ disease. Elderly patients demonstrate the highest prevalence of end-stage renal disease (ESRD) and end-stage liver disease (ESLD) [3].

This demographic shift, advances in surgical techniques, and improvements in anesthesia, critical care, and transplant medicine have all allowed for a rapid increase in the rate of liver and kidney transplantation in older patients.

As transplantation is increasingly pursued for elderly patients with end-organ disease, clinicians must be equipped to care for this uniquely vulnerable population. This population’s constellation of existing end-organ disease, high prevalence of cardiovascular and metabolic comorbidities, and frailty demand special consideration from all perioperative physicians.

This focused review regarding liver and kidney transplantation in elderly adults (aged 65 years or greater) discusses the factors that have led to an increased rate of transplantation among the elderly, the implications of age when evaluating transplant candidates, post-operative outcomes among elderly transplant recipients, ethical considerations, and potential future research directions. This review does not discuss simultaneous liver-kidney transplant recipients since this is a significantly smaller population with distinctive concerns and considerations. The data presented in this review are primarily from the United States; however, some information specific to elderly populations is included from European and Asian registries.

2. Transplants in the Elderly: A Growing Trend

The first successful kidney transplant occurred in 1953 [4], and the first liver transplant occurred in 1967 [5]. What was once a rare surgery performed in desperate circumstances is now a common occurrence. In 1988, the first year that the United States’ Organ Procurement
and Transplantation Network (OPTN) began recording data, 12,623 transplant surgeries were performed. In 2023, 46,632 transplant surgeries were performed, representing a 269% growth rate in the United States [based on OPTN data accessed on 28 March 2024].

With significant advancements in transplant surgery and medicine over this period, there has been a growing acceptance of both kidney and liver transplantation in patients aged 65 years and up. Data from both the OPTN and Eurotransplant databases demonstrate that there is a similar rate of transplant surgery in this population (Figures 1 and 2).

In the United States, in 1988, only 2.1% of all transplant recipients were 65 years old or older, and only 1.7% and 2.4% of all liver and kidney recipients, respectively, were 65 years old or older. By 2010, there had been a slow but steady increase in the rate of older transplant recipients. In 2010, 15% of all organ recipients were 65 years old or older, and 11.4% of liver recipients and 16.7% of kidney recipients were elderly. In 2023, 23.8% of all transplant recipients were 65+ years old, with 21.2% and 24.9% of all livers and kidneys, respectively, going to elderly patients (Figure 1).

This growing trend amongst recipients is also reflected by the ages of candidates on the wait lists for liver and kidney transplantations. Currently, amongst candidates for any organ, 25.5% are elderly (26,453 of 103,811 candidates). Similarly, 27.4% of liver transplant candidates (2707 of 9851 candidates) and 25.9% of kidney transplant candidates are elderly (23,118 of 89,176 candidates) [OPTN data accessed on 28 March 2024].

European data reflect a similar rate amongst kidney transplantation amongst elderly recipients. In contrast, while there has been an increase in liver transplantation for elderly recipients, the rate of liver transplantation in elderly European recipients is notably less than that in the United States (18.2% vs. 21.2% in 2023) (Figure 2).

The demographics of an aging population are not the only forces driving this increased rate of transplantation for elderly patients. Over time, there has also been a shift in the prevalence of indications for end-stage liver and kidney diseases. For example, HCV-related cirrhosis, which was seen in a predominately younger population, was formerly the most common indication for liver transplants. However, with widely available direct-acting antivirals, fewer of these patients require transplantation [6,7], and as a result, HCV is no longer the most common reason for transplant. Accordingly, metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatocellular carcinoma (HCC), which are more prevalent in the elderly, have overtaken HCV as common indications for liver transplantation [8,9]. This trend, coupled with an aging population, helps to explain the increased rate of liver transplantation in adults older than 65 years old.

Similar changes in indications for transplantation can be seen in kidney recipients. The prevalence of ESRD in elderly patients is nearly three times that of patients under the age of 65 [8]. The most common indications for renal transplant in both elderly and non-elderly patients are diabetes mellitus and hypertension. Both diseases continue to grow in prevalence and will continue to drive the progressive growth of ESRD prevalence in the elderly [9].
Figure 1. Annual percentage of all American transplant recipients, liver transplant recipients, and kidney transplant recipients aged 65 years old and older according to data from Organ Procurement and Transplantation Network [accessed on 28 March 2024]. Data are visualized with MatPlotLib software plug-in (v3.8.4, matplotlib.org) [10].

Figure 2. Percentage of European liver and kidney transplant recipients aged 65 years or greater according to data from Eurotransplant Statistics Report Library [accessed on 6 April 2024]. Data are visualized with MatPlotLib software plug-in (v3.8.4, matplotlib.org) [10].
3. Age Matters: The Implications of Aging in Transplant Recipients

When evaluating transplant candidates, physiological age is more important than chronological age. Generally, elderly individuals have increased rates of associated comorbidities, poor functional status, cognitive decline, social isolation, and frailty. However, this generality only applies to populations, and not to individuals. An individual’s age should serve as a prompt for careful consideration in each elderly patient undergoing transplantation.

Frailty can be used as an insight into physiological age and is an important consideration when evaluating potential liver or kidney recipients. Amongst the elderly, metrics such as the physical frailty phenotype (PFP) and frailty risk score (FRS) are widely used in ESRD and ESLD research [11]. Frailty, as determined by the PFP or FRS, is an independent predictor of adverse events in the post-operative period. In patients undergoing kidney transplants, frailty has been shown to be predictive of delayed graft function [12], the hospital length of stay [13], early hospital readmission [13,14], and mortality [15]. In patients undergoing liver transplants, there is relatively less research on frailty, but existing studies suggest links with an increased hospital length of stay [16], wait list mortality [17], and acute cellular rejection [18]. Despite this evidence, standardized risk assessment programs at most transplant centers do not consider formal frailty metrics, perhaps due to logistical difficulties with implementation. For example, the physical frailty phenotype (PFP), which is the most widely used frailty metric in research, requires 5–10 min for completion, sufficient space for a walking course, and repeated measurements of hand grip strength. Currently, there are efforts to develop a frailty metric based on self-reported surveys; however, the sensitivity and generalizability of these instruments remain issues [19].

Elderly patients demonstrate immune senescence, impacting their immune response to transplantation. Besides age, many other conditions contribute to a state of immune senescence: cardiac disease, cerebrovascular disease, malignancy, and infections [20]. Given the high prevalence of these comorbidities among elderly patients with end-organ disease, these patients demonstrate at least an additional 4–5 years of immune aging [20], possibly contributing to overall increased morbidity and mortality after transplant [21]. The data regarding the clinical importance of immune senescence are mixed. Overall, it appears that the relatively senescent immune system of elderly recipients decreases the risk of acute rejection. However, there may be an increased risk of post-transplant infection [21].

Regardless of the cause of their liver or kidney disease, candidates have more comorbidities and higher waitlist mortality compared to younger transplant recipients [22–26]. Overall, compared with other age groups, liver transplant recipients over sixty-five years old demonstrate similar 5-year transplant-related survival benefit [27,28].

Similarly, elderly patients with ESRD who undergo kidney transplants demonstrate improved survival when compared with those who remain on the waitlist and demonstrate equivalent survival to other adult age groups undergoing kidney transplantation [29–32]. Even at the upper limit of age, carefully selected octogenarians derive sufficient survival benefit to warrant kidney transplantation [33], suggesting that there is no concrete upper age cutoff for transplant recipients [34].

4. Evaluating an Elderly Transplant Candidate: Preoperative Considerations

A comprehensive geriatric assessment encompasses evaluations of medical comorbidities, sensory impairment, neurocognitive baseline, frailty, nutrition, and functional status. While these are important considerations for all elderly patients, they are essential components in the evaluation of the elderly transplant population.

The components of a comprehensive geriatric assessment are interrelated. A study of elderly dialysis recipients found that 46% of the study’s patients screened positive for frailty, and furthermore, frail patients had a higher risk of 12-month mortality and hospitalization. Patients with malnourishment, depression, and impairment (limited in activities of daily living) also demonstrated higher rates of 12-month mortality [35].
Neurocognitive status is also an important consideration when caring for elderly transplant recipients. In the United States, it is estimated that the prevalence of dementia in adults older than 65 years is 10.5% [36]. An interdisciplinary assessment of elderly patients at transplant centers should include the administration of a “Mini-Cog” for patients without a known history of neurocognitive impairment [37]. It is important to note the pre-operative baseline for elderly patients to anticipate post-operative cognitive dysfunction or delirium.

In addition to the known end-stage organ disease in patients undergoing transplantation, there is also a high prevalence of chronic disease and age-associated organ decline. Patients with end-stage liver or kidney disease demonstrate an especially high burden of cardiovascular comorbidities.

The relationship between liver disease and resultant cardiac dysfunction has been well documented for more than 70 years [38]. End-stage liver disease is often associated with cardiac impairment. Systemic disease can simultaneously affect the heart and liver (e.g., hemochromatosis and alcoholism). Cirrhosis-specific heart disease processes can be seen (e.g., cirrhotic cardiomyopathy and portopulmonary hypertension). Patients with end-organ failure are also at a heightened risk for common cardiovascular diseases (CVDs) that affect the general population (e.g., ischemic cardiomyopathy).

There is a high rate of CVD amongst all patients with ESRD. For patients 65–74 years old, the prevalence of CVD is 81.1% in patients receiving hemodialysis (HD), 72.6% in patients receiving peritoneal dialysis (PD), and 60.7% in patients with functioning kidney transplants. In patients greater than 75 years old, this prevalence is even higher: 85.5% among HD recipients, 79.0% among PD recipients, and 72.6% among those with functioning kidney transplants [8]. Among elderly patients with ESRD, the most common manifestations of CVD are coronary artery disease, followed by heart failure and then peripheral artery disease [8].

Pulmonary function is also frequently impaired in elderly liver and kidney transplant recipients. This is most reliably predicted by age and ASA functional status classification. Functional dependence, which is commonly seen in frail patients, is also an important risk factor for post-operative pulmonary complications [39].

Recently, there has been increased interest in examining the role of “prehabilitation” for kidney and liver recipients. “Prehabilitation” in this context refers to multidisciplinary efforts to improve functional physical activity, independence, and nutrition prior to surgery with the thought that improved physiologic reserve may improve patient outcomes. A small study among kidney transplant recipients found that prehabilitation improved physical activity significantly and may reduce the hospital length of stay [40]. A similar small, single-center study among liver transplant recipients suggested that prehabilitation may reduce costs and improve outcomes [41].

5. Post-Operative Outcomes and Considerations

Modern immunosuppressive regimens have contributed to improved outcomes and survival after transplantation, but exposure to these agents has also led to increased rates of cardiovascular complications [42]. Many commonly used immunosuppressive agents have side effects of well-recognized metabolic derangements that can be especially pronounced in elderly recipients. Of note, tacrolimus and cyclosporine are associated with hypertension, hyperglycemia, and dyslipidemia. Sirolimus may also contribute to dyslipidemia.

Metabolic syndrome, which is the constellation of obesity, insulin resistance, hyperlipidemia, and hypertension, is seen in 50% or more patients post-transplantation, with an increased age serving as an important predictor [43,44]. As a result, elderly patients incur relatively greater amounts of risk from immunosuppression when compared to younger cohorts. Because age and the presence of metabolic syndrome are both important and independent risk factors for adverse cardiovascular events in the post-transplant period, elderly patients are very vulnerable after liver or kidney transplantation.
Amongst elderly kidney transplant recipients, infection is the leading cause of death in the post-transplant period (55.2–58.5%), followed by cardiovascular disease (17.2–29.4%) [45,46]. Given the prevalence of devastating infections, as well as potential metabolic derangements, in elderly organ transplant recipients, modifications to standard immunosuppressive regimens may be necessary [47].

Graft selection for elderly kidney recipients is a key pre-operative consideration with clear impacts on post-operative outcomes. An analysis of the Eurotransplant Senior Program (ESP) revealed that elderly recipients of elderly kidney grafts have the highest risk for delayed graft function (74.1%) and the highest rejection rate (23.9%). Comparatively, elderly recipients of young kidney grafts had similar rates of delayed graft function (69.6%) and the lowest rejection rate (10.0%). Both groups had statistically similar rates of graft failure at 5 years. An impact on mortality was also seen. Among elderly patients, survival at 5 years was the lowest for recipients of elderly DCD kidneys (50.9%) compared with elderly DBD (55.0%), young DCD (68.6%), or young DBD (68.7%) kidneys [48].

When compared with kidney transplantation, elderly patients undergoing liver transplantation are at a much greater risk given the incidence of intraoperative hemorrhage, volume shifts, and metabolic derangements. Among elderly liver transplant recipients at a single center in the United States, two intra-operative factors were associated with decreased survival: a greater packed red blood cell requirement and longer warm ischemia times [24]. Yet, despite these differences that suggest more complicated operations, previous studies have shown that there is no difference in the operative time between younger versus older liver transplant recipients [24,49,50].

An analysis of 55,000 liver transplant recipients in the United States found that the main causes of death occurring within the first month after a liver transplant were cardiovascular disease (42.1%), infection (27.9%), and graft failure (12.2%). Importantly, recipient age was found to be a significant predictor of increased 30-day mortality [51]. Patients older than 65 have an increased risk of experiencing major adverse cardiac events (MI, heart failure, atrial fibrillation, stroke, or pulmonary embolus) at 30 and 90 days post-liver transplant [52]. After a liver transplant, the risk of CVD continues in the late post-transplant period as well. It is estimated that 12–16% of deaths in the late post-liver transplant period (greater than 1 year post-transplant) are attributed to CVD, though this is likely an underestimation as it excludes likely cases of sudden cardiac death [53].

The presence of MASLD pre-transplant is also an independent risk factor for 30-day mortality and early major adverse cardiac events. Given that both MASLD and cardiovascular disease are especially prevalent in the elderly liver transplant population, perioperative physicians must be vigilant when evaluating elderly transplant candidates.

6. An Ongoing Debate: Upper Age Limits for Transplantation

The trend toward increasing rates of liver and kidney transplantation in elderly patients has prompted an important research question: what is the upper limit of an acceptable age among transplant candidates? A recent meta-analysis examined outcomes regarding 1-, 3-, and 5-year survival for liver transplant recipients aged less than 70 years versus recipients aged 70 years or greater. The pooled studies, which include data collected in Europe, the United Kingdom, and the United States, revealed statistically worse 1- and 5-year survival rates for liver recipients aged 70 years or greater (78.7% vs. 86.6% and 48.9% vs. 70.1%, respectively) when compared with recipients aged less than 70 years [54]. It is important to note that these outcomes only represent specific transplantation centers.

Data from the United States Organ Procurement and Transplantation Network (OPTN) can be stratified by several age groups. The 1-, 3-, and 5-year survival rates for adults less than 65 years old (ages 18–64) and adults aged 65 years or more are collated and presented in Table 1 and Figure 3. When compared with the younger cohort, lower survival rates are observed at each interval for elderly liver and kidney recipients.
Table 1. Survival rate among American liver and kidney recipients 18–64 years of age and recipients 65+ years of age according to data from Organ Procurement and Transplantation Network [based on OPTN data accessed on 28 March 2024].

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Organ</th>
<th>Time Point</th>
<th>Number of Recipients Alive</th>
<th>Patient Survival Rate (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–64</td>
<td>Liver</td>
<td>1 Year</td>
<td>17,755</td>
<td>91.0</td>
<td>(90.6, 91.3)</td>
</tr>
<tr>
<td>65+</td>
<td>Liver</td>
<td>1 Year</td>
<td>3505</td>
<td>88.1</td>
<td>(87.0, 89.0)</td>
</tr>
<tr>
<td>18–64</td>
<td>Liver</td>
<td>3 Years</td>
<td>15,818</td>
<td>84.9</td>
<td>(84.5, 85.4)</td>
</tr>
<tr>
<td>65+</td>
<td>Liver</td>
<td>3 Years</td>
<td>2407</td>
<td>76.9</td>
<td>(75.4, 78.3)</td>
</tr>
<tr>
<td>18–64</td>
<td>Liver</td>
<td>5 Years</td>
<td>4991</td>
<td>78.4</td>
<td>(78.0, 78.9)</td>
</tr>
<tr>
<td>65+</td>
<td>Liver</td>
<td>5 Years</td>
<td>1779</td>
<td>67.5</td>
<td>(65.7, 69.2)</td>
</tr>
<tr>
<td>18–64</td>
<td>Kidney</td>
<td>1 Year</td>
<td>51,013</td>
<td>97.4</td>
<td>(97.3, 97.5)</td>
</tr>
<tr>
<td>65+</td>
<td>Kidney</td>
<td>1 Year</td>
<td>11,603</td>
<td>94.2</td>
<td>(93.7, 94.6)</td>
</tr>
<tr>
<td>18–64</td>
<td>Kidney</td>
<td>3 Years</td>
<td>39,097</td>
<td>94.7</td>
<td>(94.5, 94.9)</td>
</tr>
<tr>
<td>65+</td>
<td>Kidney</td>
<td>3 Years</td>
<td>9867</td>
<td>85.8</td>
<td>(85.1, 86.4)</td>
</tr>
<tr>
<td>18–64</td>
<td>Kidney</td>
<td>5 Years</td>
<td>32,962</td>
<td>90.2</td>
<td>(90.1, 90.4)</td>
</tr>
<tr>
<td>65+</td>
<td>Kidney</td>
<td>5 Years</td>
<td>7675</td>
<td>73.4</td>
<td>(72.6, 74.3)</td>
</tr>
</tbody>
</table>

Figure 3. Survival rates among American liver and kidney recipients 18–64 years of age and recipients 65+ years of age according to data from Organ Procurement and Transplantation Network. Error bars represent 95% confidence interval for each data point published by OPTN (and included in Table 1) [based on OPTN data accessed on 28 March 2024]. Data are visualized with MatPlotLib software plug-in (v3.8.4, matplotlib.org) [10].

It is important to note that both of these data sources focus strictly on mortality and do not include transplant-related survival benefits. Transplant-related survival benefit, not mortality, is the best metric with which to assess the utility and urgency of liver or kidney transplantation for different age groups. Transplant-related survival benefit is defined as the mean life expectancy with transplantation (to assess utility) minus the mean life expectancy without transplantation (to assess urgency). This metric better reflects the overall role of transplantation compared to waitlist mortality (which reflects urgency) and post-transplant survival (which reflects utility) alone [55–57].

At present, there is no clear consensus answer for the upper age limit for liver or kidney transplant candidates. At the authors’ medical center, there is no maximum age cutoff for liver or kidney transplant candidacy. Rather, elderly candidates are carefully evaluated on an individual basis.
Current data support the transplantation of elderly (65+ years old) recipients since they experience similar transplant-related survival benefit when compared to younger recipients [27,58]. However, further research is needed to identify transplant-related survival benefit with age groups beyond 65 years old, such as patients aged greater than 70 years old.

7. The Ethical Implications of Transplantation in the Elderly

Organs for donation represent a scarce resource, and allocation priorities must be thoughtfully considered. Transplanting organs into elderly recipients must be supported by long-term outcomes, namely transplant-related survival benefit. Thankfully, as previously discussed, a similar transplant-related survival benefit is observed amongst both young and elderly liver and kidney recipients [27,58].

For patients, the impact of transplantation is not as simple as a survival benefit. Elderly patients rate their quality of life on the basis of social contacts, dependency, health, and well-being [59]. For elderly patients to receive maximum benefit from transplantation, there should be an improvement in these quality-of-life metrics.

Several studies have demonstrated that all age groups, including elderly patients, showed improvement in quality-of-life metrics after a renal transplantation [60–62]. This benefit was magnified when compared with candidates who remained on the waitlist [62]. Similarly, improvements in quality of life were noted in liver recipients of all ages, with effects most pronounced in an area especially important to elderly patients: functional independence in self-care and mobility [63].

Furthermore, several studies support the notion that elderly patients may benefit from marginal organs that may not be acceptable for younger patients. A recent Korean study found that high-risk kidney grafts (as determined by a high kidney donor profile index) in elderly recipients were associated with a lower rate of graft failure when compared to similar grafts in younger patients [64].

Taken together, these observed outcomes further support the benefit of offering liver and kidney transplantations to patients over the age of 65. Special consideration must be given to each patient’s priorities and their risk factors as part of the pre-transplant evaluation to maximize improvements in both survival and quality of life. Further research is necessary, but it appears possible that older patients may specifically benefit from marginal, high-risk grafts that would otherwise not be offered to younger populations. This potential extension of both the donor and recipient pool represents an area for growth and further research in transplant centers.

8. Preparing for Life after Transplantation

After the initial recovery phase, patients receiving a solid organ transplantation are obligated to a lifetime of close medical attention and follow-up. For elderly patients, there are unique challenges and considerations that must be given to this stage of chronic care.

Transplant programs must consider patient and family education, post-operative care, and psychological needs when evaluating candidates and, eventually, planning hospital discharge. A recent systematic review noted that, among transplant recipients who have been discharged home, the biggest challenges they face are psychological needs, education/training, and social interaction [65].

Further, patients over the age of 65 routinely have a higher number of comorbid health conditions that must be chronically managed in addition to their transplanted organ. Special attention must be paid to medication management since polypharmacy is a common problem in this demographic. In addition, while a strong support system is important for all transplant candidates, it is especially important for elderly candidates who may require longer recovery times and increased attention at home.

Elderly patients are especially vulnerable to these psychosocial post-operative challenges, and consistently addressing these barriers may result in quality of life improvements in elderly transplant recipients.
9. Future Directions

Abdominal transplantation for elderly patients will likely continue to grow in popularity in the United States due to the aging population, the growing acceptance of older candidates, and changes in indications for surgery.

To prepare clinicians and health systems to optimally care for this unique patient population, further research is needed on the frontiers of transplantation for elderly patients. We propose several questions for future research regarding liver or kidney transplantation in elderly patients.

The process of listing a patient for transplantation is a nuanced discussion, and for elderly patients, depending on the center, this often includes discussion of frailty, the baseline functional status, and comorbidities. In this review, we discuss the outcomes of patients listed for transplantation. However, there is a paucity of research regarding the outcomes of elderly patients that centers decline to list for transplantation.

Future research might also focus on outcomes stratified by age as it relates to pre-operative organ preservation (machine perfusion or “liver in a box” strategies) or surgical techniques. Furthermore, there is a paucity of research regarding the outcomes associated with specific intra-operative management strategies (for example, the use of veno-venous bypass or extracorporeal membrane oxygenation) in patients of different ages.

Post-operatively, studies have suggested benefits to enhanced recovery after surgery (ERAS) programs, though the data on their impact specifically on elderly populations are unclear [66–69]. And with regard to donor selection or candidacy, there are unresolved questions as to the maximum donor or recipient age or age-matching of donors and recipients.

Moving forward, research that highlights the roles of different interventions in elderly transplant populations has the potential to dramatically impact clinical practice.

10. Summary

As abdominal transplantation becomes increasingly common in the United States, there has been a shift in the average age of transplant recipients. The aging population coupled with changes in indications for transplantation, improvements in transplant medicine, and an increased willingness to operate on elderly patients has led to the rapid adoption of liver and kidney transplantation in adults older than 65 years.

Elderly liver and kidney transplant recipients appear to have similar post-operative outcomes when compared to younger age groups overall [22,25,29,46,49,50,70–73]. However, existing data, for the most part, categorize patients aged 65 years or greater as simply “elderly” and, as a result, are not granular to capture the potential differences in patients aged 65–70 versus patients aged 70–80, for example. As life expectancy increases and the population continues to trend toward an older median age, further research is needed to better characterize the impact of age on transplant outcomes.

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