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Understanding the Impact of Pneumonia and Other Complications in Elderly Liver Transplant Recipients: An Analysis of NSQIP Transplant

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Background. Despite an increasing demand for liver transplantation in older patients, our understanding of posttransplant outcomes in older recipients is limited to basic recipient and graft survival. Using National Surgical Quality Improvement Program Transplant, we tracked early outcomes after liver transplantation for patients >65. **Methods.** We conducted a retrospective analysis of patients in National Surgical Quality Improvement Program Transplant between March 1, 2017 and March 31, 2019. Recipients were followed for 1 y after transplant with follow-up at 30, 90, and 365 d. Data were prospectively gathered using standard definitions across all sites. **Results.** One thousand seven hundred thirty-one adult liver transplants were enrolled; 387 (22.4%) were >65 y old. The majority of older recipients were transplanted for hepatocellular carcinoma. The older cohort had a lower lab Model for End-Stage Liver Disease and was less likely to be hospitalized at time of transplant. Overall, older recipients had higher rates of pneumonia but no difference in intensive care unit length of stay (LOS), total LOS, surgical site infection, or 30-d readmission. Subgroup analysis of patients with poor functional status revealed a significant difference in intensive care unit and total LOS. Pneumonia was even more common in older patients and had a significant impact on overall survival. **Conclusions.** By targeting patients with hepatocellular carcinoma and lower Model for End-Stage Liver Diseases, transplant centers can achieve nearly equivalent outcomes in older recipients. However, older recipients with poor functional status require greater resources and are more likely to develop pneumonia. Pneumonia was strongly associated with posttransplant survival and represents an opportunity for improvement. By truly understanding the outcomes of elderly and frail recipients, transplant centers can improve outcomes for these higher-risk recipients.

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Frailty is increasingly recognized as a predictor of waitlist mortality and posttransplant outcomes in liver transplantation.[1,2] Age is a strong driver of frailty, with patients 65 y of age or greater being far more likely to be frail than their younger counterparts.[2] As the percentage of liver transplants in the elderly rises, there is a growing need to understand the postoperative course in elderly transplant recipients.[3] The Scientific Registry for Transplant Recipients fails to capture outcomes beyond basic graft and patient survival. Single-center reports have looked at various postoperative

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complications but are limited by small sample sizes and long time frames and the burgeoning literature on frailty is largely limited to waitlisted patients.[4-10] In fact, the literature lacks a large scale, systematic evaluation of complications in the elderly liver transplant recipients.

Modeled after the National Surgical Quality Improvement Program (NSQIP), NSQIP Transplant was created through a collaboration between the American College of Surgeons and American Society for Transplant Surgeons.[11] This quality improvement platform tracks surgical complications such as death, readmissions, unplanned reoperations, and infections for up to 1-y posttransplant and has already demonstrated variation in these outcomes between transplant centers.[12] Importantly, NSQIP transplant establishes strict definitions for all variables and standardizes data collection across all sites. These factors address the shortcomings of previous studies through standardization and short study period.

Age and frailty influence decisions about who should be transplanted. It is therefore imperative that transplant centers understand the specific complications that occur after transplant and how they impact the older population. We, therefore, sought to use the power of NSQIP transplant to evaluate posttransplant outcomes in elderly transplant recipients. With this understanding, transplant centers will be able to focus their efforts on improving outcomes beyond death and graft survival while maintaining access to transplant for these patients.

MATERIALS AND METHODS

This study is a retrospective analysis of patients enrolled in NSQIP Transplant between March 1, 2017 and March 31, 2019 with follow-up extending through August 28, 2019. Recipients were followed for 1 y after transplant with dedicated follow-up at 30, 90, and 365 d. Death and graft loss were recorded as they occurred. Twenty-nine transplant centers were enrolled in the beta phase of NSQIP Transplant. All data were prospectively gathered by trained data abstractors using standard definitions across all participating sites with a goal of capturing 100% of all liver alone transplants.

The following postoperative 30-d outcomes were assessed: length of stay in the intensive care unit (ICU), total postoperative length of stay, pneumonia, hepatic artery stenosis or thrombosis, surgical site infection (SSI), portal vein stenosis or thrombosis, and overall mortality. Both hepatic and portal vein complications were defined based on the need to intervene with either operative, percutaneous, or pharmacologic management. SSI is an aggregate of any superficial, deep, or organ space infection. Pneumonia and deep vein thrombosis utilized standard American College of Surgeons proprietary NSQIP definitions.

Statistical Analysis

Basic comparisons of groups were performed using the t-test, Wilcoxon rank-sum, and chi-squared test as appropriate. Survival analysis was performed using the Kaplan Meier method; using the log-rank test to compare survival curves. The final survival analysis was performed using Cox regression and constructed using backwards stepwise selection with a *P*-value cutoff of 0.20. All analyses were performed with STATA 15.1 (StataCorp, College Station, TX).

RESULTS

Recipient Demographics

A total of 1731 adult liver transplants were performed at participating centers during this time period; 387 (22.4%) were >65 y old. Older recipients had a significantly lower BMI (28.15 versus 29.03) and were less likely to be hospitalized at time of transplant (18.9% versus 33.2%). Patients in the older cohort were far more likely to be transplanted for hepatocellular carcinoma (HCC; 53.6% versus 27.2%) and had a lower laboratory Model for End-Stage Liver Disease score at transplant (20.9 versus 24.6). Performance status was better in the older group, as defined by Karnofsky score ($P < 0.01$), but they were more likely to be diabetic (31.1% versus 22.5%). There was no significant difference between the 2 groups in gender or race (Table 1).

Donor Demographics

The older cohort received livers from donors that were older (44.9 versus 42.9 y, $P = 0.03$) and had a higher body mass index (BMI) (28.6 versus 27.8, $P = 0.04$). There was no difference in the use of donation after circulatory death donors (10.27% versus 10.28%, $P = 0.97$). There was also no difference in gender or race of the organ donors between the 2 groups.

TABLE 1.

Donor and recipient characteristics

Characteristics	Age <65 y (N = 1344)	Age >65 y (N = 387)	*P*
Age, n (%)	1344 (77.6)	387 (22.4)	
Male gender	895 (66.5%)	270 (69.8%)	0.24
BMI, mean (SD)	29.03 (6.18)	28.15 (5.03)	0.01
Race, n (%)			0.25
White	861 (64.1)	265 (68.5)	
Black	77 (5.7)	17 (4.4)	
Hispanic	171 (12.7)	35 (9.0)	
Native American	19 (1.4)	4 (1.0)	
Pacific Islander/Asian	78 (5.8)	20 (5.2)	
Unknown	138 (10.3)	46 (11.9)	
Karnofsky Score, n (%)			<0.01
10–30	395 (29.4)	57 (14.8)	
40–60	562 (41.9)	197 (51)	
70 or greater	386 (28.7)	132 (34.2)	
Diabetes	303 (22.5)	121 (31.3)	<0.01
Hospitalized, n (%)	33.2%	18.9%	<0.01
Lab MELD, mean (SD)	24.67 (12.41)	20.92 (12.59)	<0.01
Pneumonia before transplant, n (%)	45 (3.4)	4 (1.0)	0.02
HCC, n (%)	365 (27.2)	207 (53.6)	<0.01
Donor age, mean (SD)	42.98 (15.94)	44.94 (16.17)	0.03
Donor male gender, n (%)	809 (60.2)	223 (57.6)	0.36
Donor BMI, mean (SD)	27.78 (6.54)	28.59 (6.80)	0.04
Donation after circulatory death, n (%)	138 (10.27)	40 (10.28)	0.97
Donor race, n (%)			0.84
White	822 (61.2)	231 (60.8)	
Black	193 (14.4)	64 (16.5)	
Hispanic	171 (12.7)	43 (11.1)	
Native American	12 (0.9)	3 (0.8)	
Pacific Islander/Asian	47 (3.5)	14 (3.6)	
Unknown	99 (7.37)	32 (8.3)	

BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.

Overall Outcomes

Posttransplant outcomes demonstrate a higher rate of pneumonia in the older cohort (10.9% versus 7.7%, $P = 0.05$). The older cohort was more often discharged to a skilled nursing facility or rehabilitation facility (17.9% versus 12.8% $P = 0.01$). Otherwise, outcomes were largely the same between the 2 cohorts. There was no significant difference in ICU length of stay, total length of stay, SSIs, and readmissions within 30 d. The 30-d mortality was also the same between these 2 cohorts (Table 2).

There was also no difference in hepatic artery or portal venous complications. However, the younger cohort was more likely to undergo reoperation within 30 d (21.95% versus 17.05%, $P = 0.04$).

Subgroup Analysis of Acutely Ill Recipients

Given the elderly cohort was far more likely to come from home and be transplanted for HCC, we decided to perform a subanalysis focusing on performance status. In recipients with a Karnofsky score indicating the need for hospitalization (30% or less), older recipients were even more likely to develop pneumonia after transplant (19.3% versus 9.8%, $P < 0.01$). These acutely ill and elderly patients also had significantly longer ICU and overall postoperative length of stay and were far more likely to be discharged to a facility (50.0% versus 25.5%, $P < 0.01$). Despite these differences, there was no difference in 30-d mortality.

From a technical standpoint, the incidence of portal vein thrombosis was higher in the older cohort (5.3% versus 0.8%, $P = 0.01$). The rate of reoperation within 30 d was no different in subgroup analysis (29.11% versus 29.82 %, $P = 0.91$). Again, no difference in hepatic artery complications or 30-d readmissions was noted (Table 3).

Overall Recipient Survival

Simple comparison revealed no difference in overall survival between the older and younger recipient cohorts ($P = 0.28$, Figure 1). Similarly, there was no difference in overall survival, at 30 d, in the acutely ill population when comparing age groups (P-value = 0.60, Figure 2).

Given the dramatic differences in the incidence of pneumonia between groups, we further explored the impact of pneumonia on overall survival. Of all deaths recorded in the first year, 24% (21 of 87) had pneumonia in the first 30 d after transplant. This association was even more apparent in elderly recipients where 37.5% (9 of 24) of patients who died had pneumonia. Survival analysis revealed a significant difference as recipients who developed pneumonia after transplant were far more likely to die (Figure 3, $P < 0.01$), an effect that was even more pronounced in the elderly cohort (Figure 4, $P < 0.01$).

Final Cox regression analysis supports that the impact of pneumonia persists after adjusting for donor, recipient, and transplant factors. We specifically analyzed all factors included in Table 1. Any factor not included in the final model had a P-value >0.20. In the final model, pneumonia, prolonged intubation, cold ischemia time, and the total units of packed red blood cells were significant predictors of overall posttransplant survival. Age >65, recipient BMI, and donor BMI were also associated with survival but failed to reach statistical significance (Table 4).

DISCUSSION

In the 1980's era of liver transplantation, older recipients were defined by age >50.[13] Over the ensuing decades liver transplantation in older adults has increased in total numbers and as greater percentage of total liver transplants.[3] This is a trend that is likely to continue with 20% of the world's population predicted to be over the age of 65 by 2050.[14] Similarly, frailty, which is more common in the elderly, is increasingly recognized as an important predictor of outcomes. Despite these trends, there is a paucity of literature evaluating postsurgical outcomes in this population. Our study represents the first systematic attempt to study outcomes beyond death and graft survival in this population using standard definitions across multiple transplant centers.

Cursory examination of outcomes shows that older recipients do just as well as their younger counterparts. With the exception of pneumonia and likelihood of requiring skilled care after discharge, 30-d outcomes and overall survival are largely the same. However, a more in-depth analysis reveals that older recipients are being highly screened and largely limited to those with HCC who are well enough to be at home. Both lab Model for End-Stage Liver Disease and BMI were significantly lower in the older cohort. Older patients were also less likely to be hospitalized and had a far greater functional status as reflected by higher Karnofsky scores at the time of transplant. Finally, the older cohort was nearly twice as likely to be transplanted for HCC compared to their

TABLE 2.

Outcomes after liver transplantation by age

Outcome	Age <65 y (N = 1344)	Age >65 y (N = 387)	*P*
ICU LOS, mean (SD)	4.68 (8.96)	5.00 (10.37)	0.73
Total LOS, mean (SD)	14.68 (15.77)	14.70 (17.60)	0.51
Pneumonia posttransplant, n (%)	103 (7.7)	42 (10.9)	0.05
Surgical site infection, n (%)	139 (10.3)	30 (7.8)	0.13
Arterial stenosis/thrombosis, n (%)	40 (3.0)	6 (1.5)	0.12
Portal stenosis/thrombosis, n (%)	14 (1.0)	6 (1.56)	0.41
Discharged to care facility, n (%)	166 (12.8)	67 (17.9)	0.01
Reoperation at 30 d, n (%)	295 (21.95)	66 (17.05)	0.04
Readmission at 30 d, n (%)	287 (21.3)	74 (19.1)	0.34
Death at 30 d, n (%)	34 (2.53)	9 (2.33)	0.82

ICU, intensive care unit; LOS, length of stay.

TABLE 3.

Comparison of outcomes for recipients with Karnofsky 30 or less

Outcome	Age <65 y (N = 1344)	Age >65 y (N = 387)	*P*
ICU LOS, mean (SD)	7.27 (11.61)	11.08 (15.78)	0.03
Total LOS, mean (SD)	20.65 (20.68)	27.53 (22.19)	0.02
Pneumonia posttransplant, n (%)	39 (9.87)	11 (19.3)	0.03
Surgical site infection, n (%)	44 (11.14)	5 (8.8%)	0.59
Arterial stenosis/thrombosis, n (%)	9 (2.3)	0 (0)	0.25
Portal stenosis/thrombosis, n (%)	3 (0.8)	3 (5.3)	0.01
Discharged to care facility, n (%)	95 (25.5)	27 (50.0)	<0.01
Reoperation at 30 d, n (%)	115 (29.11)	17 (29.82)	0.91
Readmission at 30 d, n (%)	65 (16.5)	12 (21.1)	0.39
Death at 30 d, n (%)	18(4.6)	0 (0)	0.10

ICU, intensive care unit; LOS, length of stay.

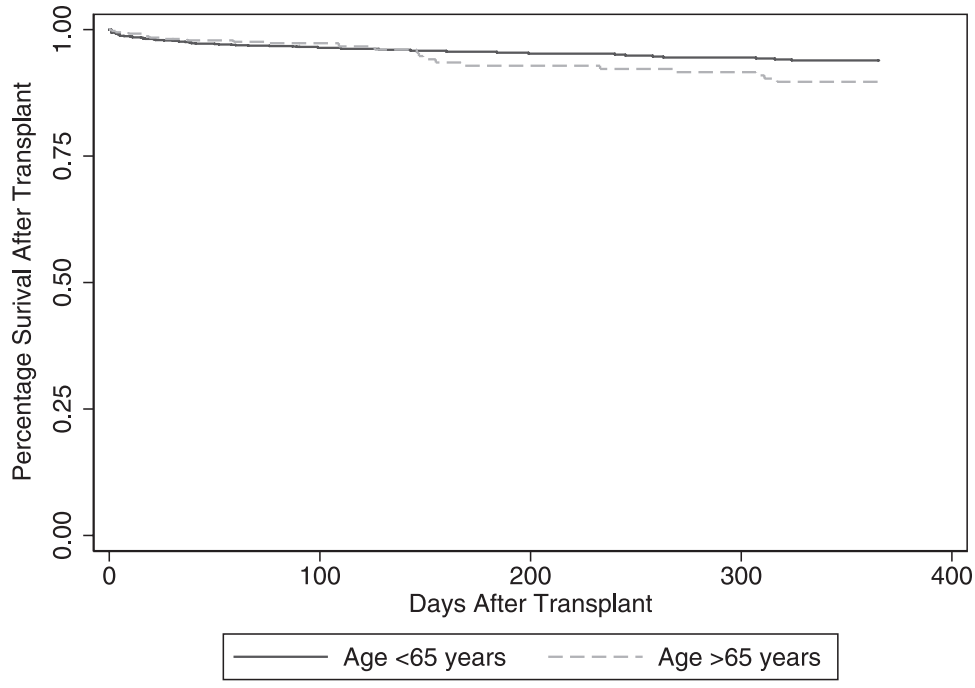

FIGURE 1. Overall survival after liver transplantation by recipient age. *P*-value = 0.28 by log-rank.

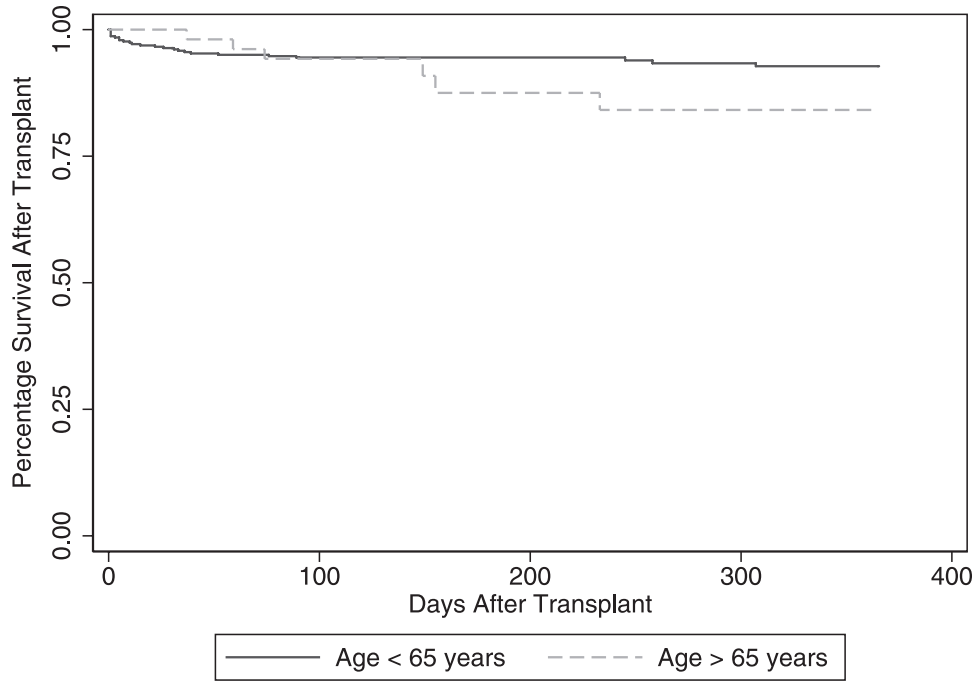

FIGURE 2. Overall survival after liver transplantation in recipients with Karnofsky score 30 or less by recipient age. *P*-value = 0.60 by log-rank.

younger counterparts. This, in part, may reflect the higher incidence of HCC in this population, but the difference is too great for this to be the only factor.[15] Altogether, these findings support a practice that selects older transplant recipients who are functional and likely to have an uneventful recovery.

When older acutely ill patients were transplanted, they were more likely to have complicated courses. Pneumonia was even more prevalent in the acutely ill elderly transplant recipient; occurring at almost twice the rate as in younger recipients. Elderly recipients were also more likely to have longer ICU and overall lengths of stay and far less likely to be discharged directly home. We also noted that portal vein thrombosis was also more common in the acutely ill and elderly population. Although the mechanism of this is unclear, these finding may be helpful in posttransplant management, raising the level of suspicion in this patient population

The most striking finding is the incidence of pneumonia in the older cohort and its significant impact on posttransplant survival. Although prior reports have demonstrated pneumonia after transplant is often deadly, no studies have been

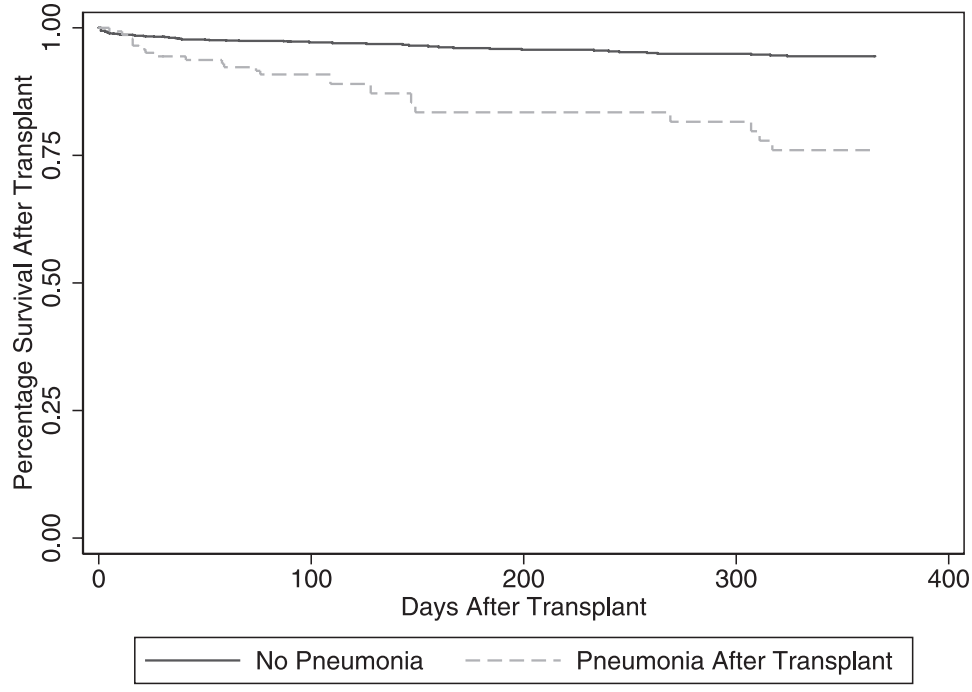

FIGURE 3. Impact of posttransplant pneumonia on survival after liver transplant. $P < 0.01$ by log-rank.

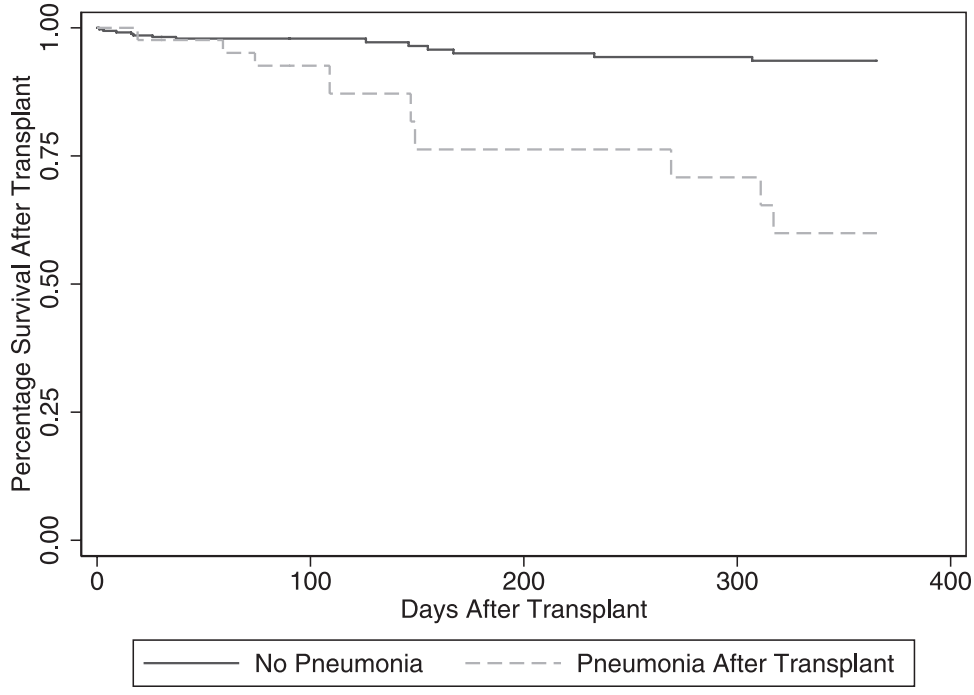

FIGURE 4. Impact of posttransplant pneumonia on survival after liver transplant in recipients 65 y of age or greater. $P < 0.01$ by log-rank.

able to study the impact of pneumonia on 1-y survival while adjusting for donor and recipient factors. In our study, older patients were far more likely to develop pneumonia posttransplant. Pneumonia was also a strong predictor of overall survival, an effect that was even more prominent in the older population. This finding is consistent with studies of pneumonia in the general population where patients over the age of 65 are more likely to develop and die from pneumonia.[14,16]

The impact of pneumonia represents an opportunity for transplant centers to improve the care of their recipients. Given the relationship between age, pneumonia, and mortality in this population, more aggressive pulmonary screening may be warranted in elderly recipients. In fact, pulmonary function tests have been associated with prolonged intubation and overall length of stay.[17] Similarly, efforts to minimize the duration of intubation after transplant may improve survival. In this cohort, 44% of recipients who developed pneumonia were intubated for >48 h after transplant. Prolonged intubation after transplant was also an independent rik factor for survival and far more important than pretransplant

TABLE 4.

Multivariable Cox proportional model for survival after liver transplant

Characteristic	Hazard ratio	95% confidence interval	*P*
Age > 65 y	1.48	0.85-2.57	0.17
Prolonged intubation	4.87	2.82-8.40	<0.01
Pneumonia posttransplant	1.82	1.01-3.27	0.04
Diabetes recipient	1.79	1.08-2.97	0.02
BMI recipient	1.03	0.99-1.07	0.09
BMI donor	0.96	0.92-1.00	0.08
Cold ischemia time, per h increase	1.06	1.00-1.12	0.03
Total PRBCs, per unit transfused	1.06	1.02-1.10	<0.01

BMI, body mass index; PRBC, packed red blood cell.

intubation, which failed to reach statistical significance in our final multivariable models. Although pretransplant pulmonary function is likely to have played a role in posttransplant intubation, working to minimize the total duration of intubation and greater focus on and optimization of pulmonary function before transplant will likely benefit potential recipients. With this in mind, we may be able to learn from our colleagues in other surgical specialties who have demonstrated improved pulmonary function and reduced pulmonary complications with prehabilitation programs.[18-20] Similar efforts may prove beneficial to elderly transplant candidates, especially those with any preexisting pulmonary issues.

NSQIP transplant offers the opportunity to explore surgical outcomes using standardized definitions across multiple institutions, providing detailed, large-volume data in a relatively short period of time. Despite the strengths of this data, our study has a number of limitations. The Karnofsky performance scale index allows classification by functional impairment, but it is somewhat subjective. Beyond Karnofsky score, the data do not provide more information on markers of frailty or pulmonary function, making it difficult to adjust for factors that may confound the relationship between pneumonia, age, and survival. Similarly, immunosuppression was not captured; making it difficult to determine if this had an impact on the frequency and severity of pneumonia. As a beta phase pilot program, data collection may have varied as sites began enrolling donors and recipients. We also limited our analysis to recipients with completed cases, which may have introduced some bias. Finally, follow-up is capped at 1 y for this program, preventing us from analyzing outcomes beyond this time period.

Overall, targeting functional patients with HCC results in excellent short-term outcomes in older transplant recipients. However, declining functional status is associated with more complex postoperative courses and warrants caution. Pneumonia after transplant is particularly concerning and is associated with overall mortality in the first year after transplant. With this improved understanding of posttransplant complications and how they impact survival, the field can work to improve outcomes and maintain access to transplantation. More thorough preoperative testing, optimization of pulmonary function and focus on enhanced recovery with shorter intubation periods, may represent opportunities for transplant centers to transplant elderly patients and while maintaining or even improving survival and decreasing morbidity. Increased age and frailty are important to the evaluation of transplant recipients, but the field must move toward a better understanding of the problems that can occur in this population. By focusing on outcomes beyond death and graft survival, NSQIP transplant provides a platform for transplant centers to understand the complications that occur after transplant and create targeted solutions to improve the lives of their recipients.

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REFERENCES

1. DeMaria S Jr, Khromava M, Schiano TD, et al. Standardized measures of frailty predict hospital length of stay following orthotopic liver transplantation for hepatocelular carcinoma. *Clin Transplant*. 2019;33:e13746.
2. Haugen CE, McAdams-DeMarco M, Holscher CM, et al. Multicenter study of age, frailty, and waitlist mortality among liver transplant candidates. *Ann Surg*. 2020;271:1132–1136.
3. Haugen CE, Holscher CM, Garonzik-Wang J, et al. National trends in liver transplantation in older adults. *J Am Geriatr Soc*. 2018;66:2321–2326.
4. Herrero JI, Lucena JF, Quiroga J, et al. Liver transplant recipients older than 60 years have lower survival and higher incidence of malignancy. *Am J Transplant*. 2003;3:1407–1412.
5. Lipshutz GS, Hiatt J, Ghobrial RM, et al. Outcome of liver transplantation in septuagenarians: a single-center experience. *Arch Surg*. 2007;142:775–781.
6. Roullet S, Defaye M, Quinart A, et al. Liver transplantation with old grafts: a ten-year experience. *Transplant Proc*. 2017;49:2135–2143.
7. Gil E, Kim JM, Jeon K, et al. Recipient age and mortality after liver transplantation: a population-based cohort study. *Transplantation*. 2018;102:2025–2032.
8. Schwartz JJ, Pappas L, Thiesset HF, et al. Liver transplantation in septuagenarians receiving model for end-stage liver disease exception points for hepatocellular carcinoma: the national experience. *Liver Transpl*. 2012;18:423–433.
9. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant*. 2014;14:1870–1879.
10. Lai JC, Rahimi RS, Verna EC, et al. Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. *Gastroenterology*. 2019;156:1675–1682.
11. Parekh J, Ko C, Lappin J, et al. A transplant-specific quality initiative-introducing TransQIP: a joint effort of the ASTS and ACS. *Am J Transplant*. 2017;17:1719–1722.
12. Parekh JR, Greenstein S, Sudan DL, et al. Beyond death and graft survival-Variation in outcomes after liver transplant. results from the NSQIP transplant beta phase. *Am J Transplant*. 2019;19:2108–2115.
13. Starzl TE, Todo S, Gordon R, et al. Liver transplantation in older patients. *N Engl J Med*. 1987;316:484–485.
14. Stupka JE, Mortensen EM, Anzueto A, et al. Community-acquired pneumonia in elderly patients. *Aging Health*. 2009;5:763–774.
15. Rich NE, Yopp AC, Singal AG, et al. Hepatocellular carcinoma incidence is decreasing among younger adults in the United States. *Clin Gastroenterol Hepatol*. 2020;18:242–8 e5.
16. Janssens JP, Krause KH. Pneumonia in the very old. *Lancet Infect Dis*. 2004;4:112–124.
17. Kia L, Cuttica MJ, Yang A, et al. The utility of pulmonary function testing in predicting outcomes following liver transplantation. *Liver Transpl*. 2016;22:805–811.
18. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer*. 2007;110:590–598.
19. Sekine Y, Chiyo M, Iwata T, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg*. 2005;53:237–243.
20. Tarumi S, Yokomise H, Gotoh M, et al. Pulmonary rehabilitation during induction chemoradiotherapy for lung cancer improves pulmonary function. *J Thorac Cardiovasc Surg*. 2015;149:569–573.