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National Assessment of Hospitalization Rates for Incident End Stage Renal Disease after Liver Transplantation

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Abstract

We examined the association of incident end stage renal disease (ESRD) after liver transplantation (LT) and resource utilization using a data linkage between the Scientific Registry of Transplant Recipients (SRTR) and claims data from the Centers for Medicare and Medicaid Services (CMS). Methods: The study cohort consisted of patients aged ≥18 years who underwent deceased donor LT between 1/1/2003 and 12/31/2010 with Medicare as primary or secondary insurance and were discharged alive from the index LT hospitalization (n=7019). The association of ESRD and post-LT hospitalization was assessed by sequential stratification, which entailed prognostic score matching of ESRD-free patients to each LT recipient at ESRD onset. The prognostic score was developed from a model of time to hospitalization and included baseline factors and hospitalization history as predictors. Results: The overall hospitalization rates for LT recipients with and without ESRD were 2.7 and 1.1 per patient-year at risk, respectively. The total number of days hospitalized patient per year was 23 in ESRD and 7 in non-ESRD LT recipients. The adjusted post-LT hospitalization rate was 97% higher after reaching ESRD compared to non-ESRD (HR=1.97; p<0.0001). Conclusions: Hospitalization rates increased significantly for LT recipients after ESRD onset. Early risk factor modification efforts targeting patients who are at high ESRD risk may reduce post-LT ESRD incidence and hence decrease morbidity and cost among LT recipients.

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Abigail R Smith, MS developed the statistical methods employed in this manuscript, and contributed to the data analysis and revision of the manuscript.

Robert M Merion, MD participated in the research design, interpretation of the results and critical revision of the manuscript.

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Introduction

End stage renal disease (ESRD) is a major public health problem affecting recipients of nonrenal solid organ transplants¹. Liver transplants (LT) account for more than half of all nonrenal organ transplants in the United States (55% from 2005 through 2014) and number well over 6,000 annually².

Since 2002, deceased donor liver allocation in the United States has been based on the Model for End-stage Liver Disease (MELD) score, which has directed more life-saving LT to recipients with decreased renal function at the time of transplant³. While the implementation of MELD-based allocation policy has resulted in improved outcomes for waitlist candidates and LT recipients, the policy led to a significant increase in the incidence of post-LT ESRD after its implementation⁴. The development of post-LT ESRD is associated with a more than 3-fold increase in the posttransplant death rate^{1,4}.

The downstream effects of ESRD in the general population include increased cardiovascular, metabolic, and infectious complications, resulting in increased morbidity, resource utilization, and healthcare costs. Total Medicare spending for ESRD patients (excluding Part D) rose to 3.2% of total spending in 2012, accounting for \$28.6 billion⁵. LT is an extremely expensive procedure, with costs in the first post-LT year alone estimated at greater than \$500,000 perpatient. LT results in greater than \$3 billion in total annual costs⁶. However, the impact of incident ESRD after LT on resource utilization is largely unknown.

It has been demonstrated that posttransplant ESRD is associated with high mortality among LT recipients⁴. That said, the experience of patients while alive is naturally very important, particularly in terms of events that are recurrent for a patient. Our primary objective in this current study is to evaluate the impact of post-LT ESRD onset on morbidity and resource utilization. Since hospital admission is an objective outcome reflective of patient morbidity, quality of life, and health resource utilization, the primary aim of our current study was to examine the association between post-LT ESRD and hospitalizations rates.

Methods and Material

Our study population features the linkage of files derived from 2 health-related databases. The analysis utilizes a recently developed extension of sequential stratification⁷ to recurrent event data^{8,9}, which essentially contrasts the hospitalization rate of each post-LT ESRD patient with the patient's (counterfactual) ESRD-free experience.

Data sources

Data used for this study were derived from a linkage of transplant data from the Scientific Registry for Transplant Recipients (SRTR) and Medicare eligibility and claims data from the Centers for Medicare & Medicaid Services (CMS).

The SRTR data system has a uniform structure and includes data on all donor, waitlisted candidates, and transplant recipients in the US. Patient records are submitted to the Organ Procurement and Transplantation Network (OPTN) by transplant centers. The candidate registration information is provided by each transplant center at the time of placement on the

waitlist. Transplant recipient registration information is provided by the transplant center at the time of LT, with post-LT follow-up data provided at 6 months, 1 year, and annually thereafter. The SRTR supplements information on vital status with data on deaths from the Social Security Death Master Files and CMS, and supplements ESRD onset information using data from CMS¹⁰. The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

CMS data contain enrollment and utilization data for each beneficiary. The beneficiary summary file indicates the periods of time a person was eligible for Medicare coverage. The MedPAR File contains inpatient hospital and skilled nursing facility (SNF) final action stay records. Each MedPAR record represents a stay in an inpatient hospital or SNF and includes dates of admission and discharge. Each MedPAR record may represent 1 claim or multiple claims, depending on the length of a beneficiary's stay and the amount of services used throughout the stay.

Record Linkage

A list of adult deceased donor LT recipients from 2003 – 2010 was sent from the SRTR to CMS-Contractor Buccaneer to link to records in the CMS data. The linkage was performed based on: social security number, first and last name, sex, and date of birth. Buccaneer produced a crosswalk file that allowed us to match records in SRTR and CMS data using de-identified patient identifiers.

Study population

This study included age 18years recipients of primary, deceased donor LT, between January 2003 and December 2010 that were discharged from the initial transplant hospitalization alive with the index graft. Living donor LT, multi-organ transplant including simultaneous liver- kidney transplants, recipients with ESRD prior to discharge from the transplant hospitalization, and those without Medicare insurance at time of transplant and discharge were excluded. Hospitalization admission dates were extracted from the records in the MedPAR file.

Our primary outcome was post-LT hospitalization. Time at risk began at discharge from initial transplant hospitalization and continued until the earlier of death or end of study. Any periods of time for which recipients were not eligible for Medicare coverage were excluded from the analysis. Time spent in the hospital was not considered as time at risk. Records where a discharge was followed by an admission on the same day were counted as 1 hospitalization event.

Analytic approach

Descriptive statistics—Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as frequencies and percentages. Overall hospitalization rates were calculated as the total number of hospitalizations divided by the number of patient years at risk. We also examined hospitalization rates by various follow-up time intervals (0-6 months, 6 months-1 year, year 2, year 3, year 4, year 5, 6 or more years)

from ESRD onset. Note that these post-LT follow-up time intervals were used only for the purposes of our descriptive analysis and play no role in the rate regression modeling described in the next subsection. The missingness of various covariates in the SRTR data varied from 0-7% except for serum sodium. We did not include sodium in our analysis due to the lack of serum sodium data from 1/1/03 to 10/31/04. For modeling purposes, missing values were imputed with a single mean value imputation and a missingness dummy covariate. The final prognostic score model included only 1 variable with any missing data (<2% missing). We also performed a complete case sensitivity analysis.

Modeling hospitalization rates—Modeling for this analysis used sequential stratification^{7,11,12} applied to the proportional rates method of evaluating recurrent events over time. Sequential stratification evaluates a time dependent event or factor of interest (ESRD) in the presence of other time dependent characteristics (risk of hospitalization)⁷. A separate stratum was created for each subject that developed ESRD. Each stratum included the subject that developed ESRD and a matched set of subjects that did not have ESRD at the same number of days after discharge from the transplant hospitalization⁷. Subjects were matched based on a hospitalization prognostic score (described below) that predicts the rate of hospitalization. This sets up a comparison between an index subject that developed ESRD and subjects with a similar rate of hospitalization to the index subject just before they developed ESRD. The model included a covariate for the difference in prognostic score between the index ESRD subject and the matched subjects in the strata. Nonindex subjects were censored if they developed ESRD after entry into the stratum and they started a new stratum as the index subject at that time. Note that the sequential stratification method we used¹³ is distinguished from previous versions of sequential stratification¹⁴ due to the accommodation of recurrent events and the use of a hospitalization prognostic score in place of covariate adjustment. We use the terms effect and association interchangeably when reporting the results from our models. However, since we are using observational data the term effect is not meant to imply a causal relationship.

Predictors of hospitalization and development of hospitalization prognostic score—The hospitalization prognostic score was developed from a model of time to hospitalization and included baseline factors and hospitalization history as predictors. The covariates included were: number of hospitalizations, cumulative days hospitalized, recipient age, race, sex, height, weight, BMI, diagnosis, diabetes, medical condition at transplant, bilirubin, creatinine, INR and donor factors (age, sex, race, height, weight, BMI, cause of death) and cold ischemia time. Backward elimination was used to reach a parsimonious model. Sensitivity analyses were also performed using best subsets model selection and using the renal risk index and donor risk index in place of individual covariates to adjust for potential recipient and donor confounders.

The hospitalization prognostic score was calculated for each recipient as the linear combination of parameter estimates and patient characteristics. Histograms of the hospitalization prognostic score for the index subject and the average hospitalization prognostic score for matched subjects in a stratum were compared side by side to evaluate how closely they matched.

With respect to interactions, we assessed whether the effect of ESRD on hospitalization depended on either the hospitalization prognostic score or time since ESRD onset.

Based on the patients with ESRD onset, and their prognostic score-matched counterparts, we plotted the hospitalization rates over time. For the ESRD curve, the time axis represented time since ESRD onset; for the matched comparator patients, the time axis was time since ESRD onset for the index ESRD patient to whom they were matched. Rates for the ESRD curve were computed using hospitalizations divided by patient-years at risk. For the matched comparator group, we first averaged within matched set, then took the ‘average of the averages’ in order to preserve the equality of distributions of both pre-‘ESRD’ follow-up time and prognostic score.

Modeling length of stay

To quantify the effect of ESRD on hospital stay per admission, we used a multiplicative means model, fitted using generalized estimating equations. The response was the number of days hospitalized, and the main covariate of interest was the ESRD status of the recipient at admission. The model adjusted for time since discharge from transplant hospitalization, length of transplant hospital stay, recipient age, sex, race, BMI, diagnosis, functional status, diabetes, life support, ascites, albumin, creatinine, bilirubin, dialysis, INR, status 1, portal vein thrombosis, TIPSS, donor age, sex, race, height, cause of death, donation after cardiac death (DCD), split liver, shared organ, and cold ischemia time. A robust ‘sandwich’ estimator was used to estimate the standard errors, in order to account for the correlation among repeated hospitalizations within patient. All statistical analyses were carried out using SAS (v9.4; SAS Institute: Cary, NC). Results with a 2-sided p-value <0.05 were considered statistically significant.

The University of Michigan Institutional Review Board approved this study.

Results

Study population

Figure 1 shows the study cohort. There were 41,192 adult recipients of deceased donor liver transplants in the United States during the study period. Of these, 9,753 recipients were eligible for Medicare coverage for their transplant and at the time of discharge from the index transplant hospitalization. We excluded 136 subjects who received a previous transplant, 740 for death or graft failure during initial hospitalization, 1657 without a transplant hospitalization record covering the date of the transplant, and 201 subjects with prevalent ESRD at LT. The final study group consisted of 7,019 recipients. The baseline characteristics of the study population are shown in Table 1.

Hospitalization rates

Median follow-up time was 3 years. Two hundred seventy-seven subjects in the study developed ESRD at a median of 1.9 years post-LT. The mean baseline renal risk index¹⁵ was higher for recipients who developed ESRD than for those that did not (4.2 vs. 2.3; p<0.001).

Figure 2 shows the distribution of the number of hospitalizations per recipient during the study period. The overall hospitalization rates for recipients with and without ESRD were 2.7 and 1.1 per patient year at risk, respectively. The total days hospitalized per patient per year were 23 in ESRD and 7 in non-ESRD LT recipients.

Predictors of hospitalization

Table 2 shows the predictors of hospitalization rates. These factors (Table 2) were included in the development of a hospitalization prognostic score. The covariates related to prior hospitalization were strongly associated with future hospitalizations. Every additional prior hospitalization was associated with a 13% higher rate of future hospitalizations. In terms of (previous) total days in the hospital, every additional week hospitalized was associated with a 3.9% increased rate of (future) hospitalization.

Distribution of hospitalization prognostic scores for ESRD and non-ESRD LT recipients

Figure 3 displays the distribution of hospitalization prognostic scores for index ESRD subjects and the subjects matched to them in the strata. The strata were formed by matching subjects at the time of ESRD onset with subjects who had not developed ESRD and were the same number of days postdischarge from their initial transplant hospitalization and had a prognostic score within 0.05 of the index ESRD subject. As expected, the distributions of hospitalization prognostic scores for index ESRD subjects and matched non-ESRD subjects were extremely similar.

Effect of incident ESRD on hospitalization

Based on the sequential stratification model, recipients who developed ESRD had almost twice the rate of hospitalization after onset of ESRD than non-ESRD recipients with a similar hospitalization rate at the time of ESRD onset for the index subject (HR=1.97, $p<0.0001$). Results from the complete case analysis and alternative sets of covariates for the prognostic model were consistent with the main analysis.

We performed a sensitivity analysis, and found that the test of interaction between ESRD and quartile of hospitalization prognostic score was not statistically significant ($p=0.98$), indicating that the increased rate of hospitalization due to ESRD did not depend on the underlying rate of hospitalization.

Next, we tested the interaction between incident ESRD by time since ESRD on the rate of hospitalization. The interaction for incident ESRD by time was highly nonsignificant ($p=0.83$) suggesting that among incident ESRD subjects time since ESRD did not affect the relative rate of hospitalization.

Figure 4 displays hospitalization rates over time stratified by ESRD status. The ESRD line is based on LT recipients who experience ESRD, with the time origin being time of ESRD onset. The 'non-ESRD' line is based on an average across matched sets of the matched comparator patients. The ESRD and non-ESRD rates are highest soon after the time of ESRD (ie time of matching), and decreasing steadily thereafter. The lines appear to be

parallel to each other, indicating that the difference in ESRD and non-ESRD hospitalization rates is approximately constant over time.

Effect of ESRD on length of hospital stay

The distributions of the lengths of stay per post-LT hospitalization for subjects with and without ESRD are shown in Figure 5. The median length of stay was 5 days for recipients with ESRD and 4 days for recipients without ESRD. Based on an adjusted length-of-stay model, recipients with ESRD spent 1.30 times as many days in the hospital (per admission) as recipients without ESRD ($p<0.001$). This model was adjusted for the time since discharge from transplant hospitalization and the length of transplant hospital stay in addition to numerous recipient, donor and transplant characteristics as specified in the Methods section.

Discussion

Using data from 2 large national databases (Scientific Registry of Transplant Recipients (SRTR) and the Centers for Medicare and Medicaid Services (CMS), our study found that post-LT hospitalization rates were significantly elevated by onset of post-LT ESRD. In addition to recipient and donor factors, previous hospitalization history as well as number of days hospitalized were associated with increased rate of future hospitalization.

We and others have previously shown that post-LT ESRD was associated with higher death rates among LT recipients with 3.36 folds higher adjusted hazard of death⁴¹⁶⁻¹⁸. Building upon our previous results of prediction of post-LT ESRD risk using the renal risk index and post-LT ESRD associated mortality, in this study, we examined the morbidity associated with ESRD through examination of hospitalization rates. Hospitalization is an objective end-point associated with morbidity, resource utilization, and quality of life. Measures of the frequency of hospitalization have the potential to inform efforts to control escalating medical costs, and to play an important role to identify targets for more cost-effective healthcare. In 2012, the hospitalization rate for ESRD patients in the United States was 1.78 hospitalizations (and an average of 11 hospital days) per patient year¹⁹.

Our study found a substantial relative risk (adjusted HR=1.97) of hospitalization among patients who developed ESRD compared to non-ESRD patients at similar risk of being hospitalized. Hospitalization accounts for approximately 35% of total Medicare expenditures for ESRD patients. In our study, the overall hospitalization rate among LT recipients with ESRD was 2.72 per patient-year, 53% higher than the hospitalization rate for the general ESRD population in the US. LT recipients with ESRD spent 23 days per patient year in the hospital, more than twice that of the broader ESRD population.

Our results do not imply that candidates at the elevated risk of incident post-LT ESRD should be denied LT. Liver allocation is based upon urgency. Although high risk candidates awaiting LT may develop incident ESRD overtime after LT, they do receive a survival benefit from LT. Our results quantify the elevated risk of hospitalization associated with incident ESRD among LT recipients. The downstream effects of increased hospitalization rates include increased resource utilization, high morbidity and healthcare costs affecting quality of life, and other patient-centered outcomes. Understanding and awareness of high

rates of hospitalization among these patients may result in implementation of innovative interventions such as discharge planning with regular follow-up using technology based upon the principles of multidisciplinary chronic disease management. This would result in prevention or reduction in hospitalizations, thus leading to improved patient care and hence, decreased resource utilization, and improved quality of life.

Our objective was to make each ESRD patient comparable to the patients in his/her stratum at the time of ESRD onset (not under-adjusting), but not force the comparison to be among equals thereafter (avoiding over-adjusting). Therefore, we compared each index ESRD subject to non-ESRD subjects with similar baseline rates of hospitalization using a newly developed recurrent event version of sequential stratification. In describing the rationale for using the sequential stratification method it is useful to consider limitations inherent to alternative approaches. First, an analysis using only baseline (time 0) covariates (ie combined with a time-dependent 0/1 ESRD indicator) would be generally subject to time-dependent confounding, unless hospitalization history did not predict ESRD onset (which it does). The result would be to exaggerate the effect of ESRD on hospitalizations. Second, a traditional time-dependent analysis which adjusted for time-dependent hospitalization history (eg through a time-dependent previous-hospitalizations counter) would tend to attenuate the effect of ESRD onset, unless hospitalizations within-patient were uncorrelated (and they are correlated). Therefore, the baseline-adjustment covariate approach fails to adjust adequately for hospitalization history leading up to ESRD (hence over-estimating the ESRD effect), while the time-dependent approach over-adjusts (biasing the ESRD effect towards the null). The sequential stratification approach strikes the appropriate balance in terms of adjustment for time-dependent factors by essentially customizing the comparison group for each ESRD patient (at the time of ESRD onset). Furthermore, the hospitalization prognostic scores computed from significant predictors of hospitalization rates were used to match the ESRD subjects at the time of ESRD onset with comparable non-ESRD subjects with similar duration of follow-up.

The limitations of our study include the observational retrospective design that results in the potential for bias due to patient selection and unmeasured patient characteristics. Although large observational studies derived from administrative and clinical data bases have proven very useful for health services research, the accuracy of these databases in terms of data quality and completeness are often questioned. Our study population consists of the approximately 25% of LT recipients with Medicare as a primary or secondary payer. Therefore, these results may not be generalizable to all LT recipients. In order to address this limitation, we compared the baseline characteristics of LT recipients with Medicare as primary or secondary insurance to nonMedicare recipients, and except for slightly older age among those with Medicare as primary and secondary insurance, all other factors were similar. The linkage between the 2 databases (SRTR and CMS) provided us with a large sample size of over 7,000 LT recipients, giving us adequate power for hypothesis testing and covariate adjustment that may not be possible with smaller data sources. LT recipients are not well represented in the nationwide inpatient sample because of the small number of LT performed each year, and single center studies lack the power to build robust models. The novelty of this linkage is that the SRTR data provides the pre, peri, and posttransplant data of recipients, donors, and centers, and the CMS claims data provides data on hospitalization

including the date of admission, discharge, diagnoses, comorbidities, and cost. Despite the shortcomings, this is the best data source to study the burden of post-LT hospitalization among ESRD recipients.

In conclusion, the rate of hospitalization increases after a LT recipient develops ESRD, independent of the rate prior to ESRD. Reducing the incidence of post-LT ESRD using active chronic kidney disease surveillance and targeted intervention among LT recipients may ameliorate the burden of hospitalization among LT recipients.

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Abbreviations

CMS	Centers for Medicare and Medicaid Services
ESRD	End stage renal disease
LT	Liver transplantation
MELD	Model for End-stage Liver Disease
OPTN	Organ Procurement and Transplantation Network
SRTR	Scientific Registry of Transplant Recipients

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Study Population

Figure 1.
Flow diagram describing the selection of the study population

Figure 2.
Histogram of number of hospitalizations per patient during follow-up.

Figure 3.

Histograms for prognostic scores among index ESRD subjects (left panel) and matched non-ESRD recipients (right panel).

Footnote: The input records for the ESRD subjects (left) include the prognostic scores of patients experiencing ESRD onset, as computed at the time of onset. Input records for the matched non-ESRD patients are stratum averages, with each stratum representing the set of patients matched to a given index ESRD patient.

Figure 4.

Hospitalization rates by follow-up time* and ESRD status.

Footnote: * Time at risk begins at ESRD onset for subjects with ESRD or stratum entry for matched non-ESRD subjects

Figure 5.
Histograms for length of hospital stay (days) for subjects by ESRD status.
Footnote: LT recipients with ESRD (left panel) and LT recipients without ESRD (right panel).

Table 1

Baseline characteristics of study population at the time of liver transplantation

Characteristic	Median (IQR) or n (%) (n=7,019)
Age at TX	59 (52-66)
Males Females	4,672 (67%) 2,347 (33%)
White Black Asian Hispanic/Latino Multi-racial/other	5,191 (74%) 527 (8%) 270 (4%) 956 (14%) 75 (1%)
Lab MELD at LT	17.0 (13.0-23.0)
HCV Cholestatic Non-cholestatic HCC Other liver disease	2,502 (36%) 518 (7%) 2,203 (31%) 1,210 (17%) 586 (8%)
Diabetes	1,979 (28%)
Hospitalized in ICU Hospitalized not in ICU Ambulatory	460 (7%) 910 (13%) 5,649 (80%)
Body Mass Index	27.8 (24.6-32.0)
Renal Risk Index	1.56 (0.98-2.72)
Donor Risk Index	1.45 (1.23-1.75)

Table 2

Hospitalization prognostic score model

Parameter	Estimate	Hazard Ratio	p-value
Recipient factors			
Number of hospitalizations	0.125	1.13	<.0001
Number of days hospitalized	0.005	1.01	<.0001
Age at LT (Ref: 50-55 years)			
< 40 years	0.070	1.07	0.23
40 to 50 years	0.033	1.03	0.39
55 to 60 years	-0.053	0.95	0.14
60 to 65 years	0.008	1.01	0.82
>65 years	-0.072	0.93	0.02
Hepatitis C	0.095	1.10	<.0001
African American (Ref: all others)	0.154	1.17	<.0001
Diabetes	0.135	1.14	<.0001
Log _e (albumin)	-0.131	0.88	0.003
Log _e (creatinine)	0.125	1.13	<.0001
Log _e (bilirubin)	-0.026	0.97	0.02
Donor and Transplant factors			
Donor age (18-39 years)			
<18 years	-0.049	0.95	0.26
40 to 50 years	0.058	1.06	0.08
50 to 60 years	0.110	1.12	<.0001
60 to 70 years	0.089	1.09	0.01
>70 years	0.127	1.14	0.003
Donation after cardiac death	0.109	1.12	0.02
Donor height (cm)	-0.002	1.00	0.01
Regional share (ref: local)	0.032	1.03	0.19
National share (ref: local)	0.122	1.13	0.0009
Split liver transplant	0.176	1.19	0.02