Patient-Specific Prediction of ESRD after Liver Transplantation

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ABSTRACT

Incident ESRD after liver transplantation (LT) is associated with high post-transplant mortality. We constructed and validated a continuous renal risk index (RRI) to predict post-LT ESRD. Data for 43,514 adult recipients of deceased donor LT alone (February 28, 2002 to December 31, 2010) were linked from the Scientific Registry of Transplant Recipients and the Centers for Medicare and Medicaid Services ESRD Program. An adjusted Cox regression model of time to post-LT ESRD was fitted, and the resulting equation was used to calculate an RRI for each LT recipient. The RRI included 14 recipient factors: age, African-American race, hepatitis C, cholestatic disease, body mass index≥35, pre-LT diabetes, ln creatinine for recipients not on dialysis, ln albumin, ln bilirubin, serum sodium<134 mEq/L, status-1, previous LT, transjugular intrahepatic portosystemic shunt, and acute dialysis at LT. This RRI was validated and had a C statistic of 0.76 (95% confidence interval, 0.75 to 0.78). Higher RRI associated significantly with higher 5-year cumulative incidence of ESRD and post-transplant mortality. In conclusion, the RRI constructed in this study quantifies the risk of post-LT ESRD and is applicable to all LT alone recipients. This new validated measure may serve as an important prognostic tool in ameliorating post-LT ESRD risk and improve survival by informing post-LT patient management strategies.

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Chronic renal failure (CRF) and ESRD are major public health problems.[1] They also represent a major form of morbidity after nonrenal solid organ transplant and are associated with high post-transplant mortality, increased resource utilization, and high cost.[2–5]

Candidates with end stage liver disease on the waiting list are prioritized for deceased donor liver transplantation (LT) based on the Model for End-Stage Liver Disease (MELD) score.[6] The MELD score is highly associated with the risk of death in the absence of an LT. It has served as the basis for liver allocation in the United States since February of 2002 in accordance with federal regulations emanating from an Institute of Medicine recommendation that deceased donor livers should be allocated based on "objective and measurable criteria of urgency." The MELD score is computed using serum creatinine, serum bilirubin, and the international normalized ratio (INR) of the prothrombin time as follows[7,8]:

$$MELD = 10\times(0.957\ \log_e\ creatinine + 0.378\ \log_e\ bilirubin + 1.12\ \log_e\ INR + 0.643)$$

Recipients of deceased donor LT in the pre-MELD era had an 18% cumulative incidence of post-LT CRF at 5 years.[2] In examining the MELD equation, serum creatinine has the greatest impact on the overall score, reflecting the influence of renal dysfunction on waitlist mortality in end stage liver disease candidates.[9]

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However, MELD score is unable to differentiate between candidates with severe synthetic dysfunction of liver and well preserved renal function and candidates with preexisting renal disease in the setting of well preserved liver function. An unintended consequence of MELD-based policy was a 15% higher relative risk of post-LT ESRD among LT recipients compared with the pre-MELD era.[5] Consequently, the post-LT ESRD incidence rate has risen significantly since the implementation of MELD-based allocation policy.[5]

Our aim was to construct a risk score based on recipients' risk factors to identify the LT recipients at elevated risk for post-LT ESRD among recipients of LT alone.

RESULTS

Patient Characteristics

A total of 43,514 candidates met the inclusion criteria and received deceased donor LT during the study period (Figure 1). Table 1 shows the recipient characteristics at LT.

The median donor age was 43 years (interquartile range [IQR]=25–55), 60% were men, median cold ischemia time was 7 hours (IQR=5.2–9.0), and 4% were donation after cardiac death (DCD) donors.

Incidence and Predictors of Post-LT ESRD

There were 1812 ESRD events. The post-LT ESRD incidence rate among recipients was 15.0 per 1000 patient-years. Table 2 shows the recipient risk factors independently associated with the post-LT ESRD.

Donor risk factors significantly associated with post-LT ESRD included age 50–59 years versus reference age 18–39 years (hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.03 to 1.34; P=0.02), age 60–69 years (HR, 1.29; 95% CI, 1.10 to 1.51; P=0.002), age≥70 years (HR, 1.31; 95% CI, 1.06 to 1.62; P=0.01), and DCD (HR, 1.45; 95% CI, 1.17 to 1.80; $P<0.001$). Each additional 1 hour of cold ischemia time (HR, 1.02; 95% CI, 1.01 to 1.06; $P<0.001$) was also significantly associated with a higher risk of post-LT ESRD. The type of calcineurin inhibitor (CNI) and use of antibody induction after LT were not associated with the post-LT ESRD.

Renal Risk Index

The Cox model for new onset post-LT ESRD onset included 14 recipient factors significantly associated with post-LT ESRD: age at LT, African-American race, hepatitis C, cholestatic disease, body mass index (BMI), pre-LT diabetes, serum creatinine, creatinine slope, serum albumin, serum bilirubin, serum sodium, status-1, previous LT, transjugular intrahepatic portosystemic shunt (TIPSS), and acute dialysis. The slope of creatinine from the time of listing to LT was significant (HR, 0.90; 95% CI, 0.86 to 0.94 $P<0.001$). However, a sensitivity analysis testing the final model with and without creatinine slope did not meaningfully alter the HR for the other covariates, and therefore, it was not included in the final renal risk index (RRI) model. The final multivariable RRI model, as shown below, was also adjusted for confounding donor factors:

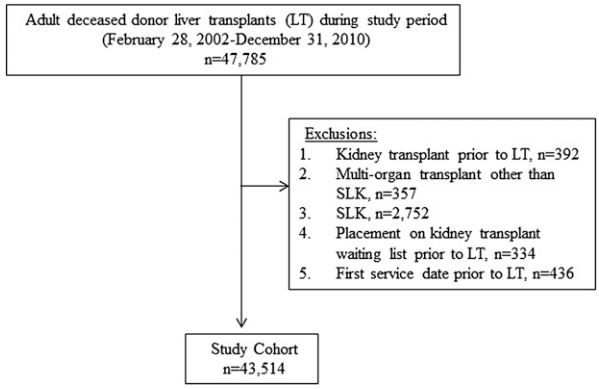

Figure 1. Description of cohort. Adult deceased donor LT recipients transplanted between February 28, 2002, and December 31, 2010. LT, liver transplant; SLK, simultaneous liver and kidney transplant.

Table 1. Recipient characteristics of the cohort (n=43,514)

Characteristic	n (%) or Median (Quartile 1–Quartile 3)
Age at LT (yr)	54 (48–60)
Men	29,453 (67.7%)
Race	
White	31,671 (72.8%)
African American	3967 (9.1%)
Hispanic	5446 (12.5%)
Asian	2076 (4.8%)
Other	354 (0.8%)
Diagnosis	
Hepatitis C	19,143 (44.0%)
Cholestatic liver disease	4378 (10.1%)
Pre-LT diabetes	9359 (21.5%)
Status-1 at LT	2468 (5.7%)
BMI	27.4 (24.0–31.4)
Laboratory MELD score	19 (14–27)
Serum creatinine at LT	1.1 (0.8–1.5)
Serum bilirubin at LT	3.8 (1.9–9.5)
INR at LT	1.6 (1.3–2.1)
RRT at LT	2231 (5.1%)
RRT≤6 wk at LT	2203
RRT>6 wk at LT	28
Nonsteroid induction therapy used	9287 (21.3%)
Steroids part of initial maintenance immunosuppression regimen	33,634 (77.3%)

$$RRI = \exp^{[(0.00688\times(\textit{recipient age}-53))+(0.4292\ \textit{if African American})+(-0.3725\ \textit{if cholestatic})+(0.2711\ \textit{if HCV})+(0.7111\ \textit{if diabetic})+(0.2450\ \textit{if BMI}\geq 35)+(1.2522\times\ln(\textit{creatinine})\textit{if not on dialysis})+(-0.1525\times\ln(\textit{bilirubin}/3.5))+(-0.3851\times\ln(\text{albumin}/2.9))+(-0.3706\ \textit{if sodium}<134)+(-0.2671\ \ \textit{if status-1})+(0.4359\ \textit{if previous LT})+(0.3129\ \textit{if TIPSS})+(1.9097\ \textit{if on dialysis})]}.$$

Table 2. Multivariable model of LT recipient factors significantly associated with post-LT ESRD

Factor	HR (95% CI)	*P* Value
Age (per 10 yr)	1.07 (1.02 to 1.12)	0.01
African American (reference: white)	1.54 (1.34 to 1.77)	<0.001
BMI≥35 kg/m^2	1.28 (1.84 to 2.25)	<0.001
Cholestatic disease (reference: no)	0.69 (0.56 to 0.85)	<0.001
Hepatitis C (reference: non-hepatitis C)	1.31 (1.19 to 1.45)	<0.001
Recipient diabetes	2.04 (1.84 to 2.25)	<0.001
ln creatinine (for nondialysis)	3.50 (3.22 to 3.81)	<0.001
ln bilirubin	0.86 (0.82 to 0.90)	<0.001
ln albumin	0.68 (0.57 to 0.82)	<0.001
Sodium<134 mEq/L (reference: ≥134 mEq/L)	0.69 (0.60 to 0.80)	<0.001
Status-1	0.77 (0.62 to 0.95)	0.02
TIPSS	1.37 (1.18 to 1.59)	<0.001
Previous LT	1.55 (1.31 to 1.82)	<0.001
Acute dialysis at LT	6.75 (5.79 to 7.90)	<0.001

Model also adjusted for donor age, sex, donation after cardiac death, cold ischemia time, and local versus shared (regionally or nationally) organ. HCV.

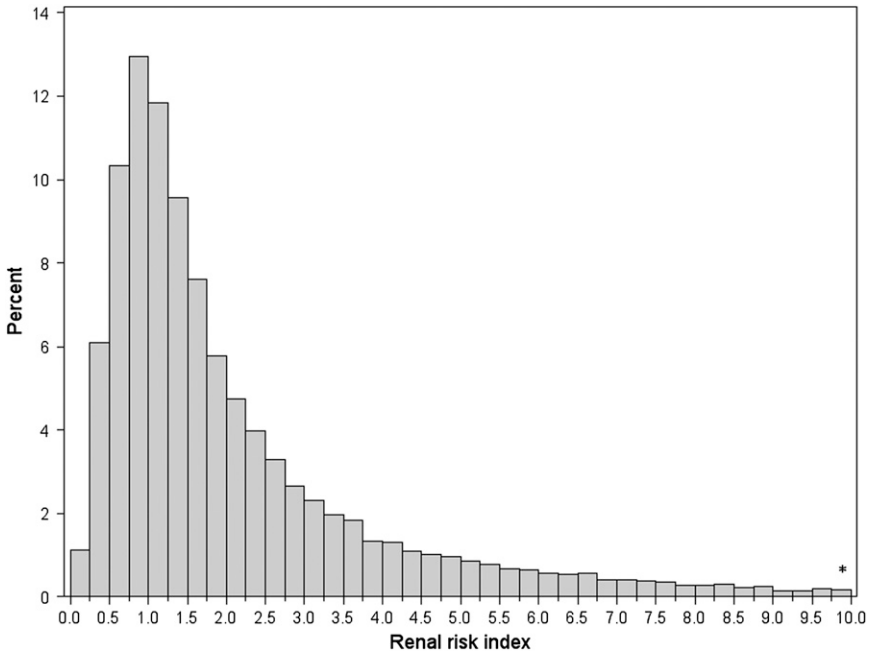

Figure 2. Distribution of RRI based on recipient characteristics at the time of liver transplantation. *Represents 97% of the RRI distribution.

The baseline characteristics of reference LT recipient (RRI=1.00) at LT were 53 years old, not African American, noncholestatic disease, hepatitis C-negative, BMI<35 kg/m^2, nondiabetic, serum creatinine=1.0 mg/dl, serum albumin=2.9 g/dl, serum bilirubin=3.5 mg/dl, serum sodium≥134 mEq/L, not status-1, no previous LT, no history of TIPSS, and not on dialysis at LT.

For each candidate, the RRI was calculated as the product of that patient's covariate-specific HRs. The calculated RRI represents the risk of ESRD for that recipient compared with the reference patient. For example, a patient with RRI=1.26 has a 26% higher risk of developing post-LT ESRD compared with the reference patient with RRI=1.00.

Model Validation

The index of concordance (IOC) for the model derived from the entire dataset was 0.765 (95% confidence interval, 0.75 to 0.78). The IOC obtained from 10 random cross-sections of the validation cohort was 0.753–0.770. The mean IOC of 10 validation datasets was 0.763, indicating that, on average, the model predicted the correct ordering 76.3% of the time among pairs of subjects whose time to ESRD could be ordered.

Distribution of RRI

Figure 2 shows that the cohort did not have a normal distribution of RRI. LT recipients were stratified by RRI decile (~4350 LT recipients/decile) to examine patient characteristics and outcomes by RRI decile. The clinical characteristics of patients in each decile are shown in Table 3.

RRI and Cumulative Incidence of Post-LT ESRD

Figure 3 shows the cumulative incidence of post-ESRD by decile. The reference LT recipient (RRI=1) is in the third decile. The 1-, 3-, and 5-year cumulative incidences of post-LT ESRD for the decile containing the reference LT recipient were 0.8%, 1.4%, and 2.3%, respectively. In contrast, the cumulative incidences of post-LT ESRD for recipients were 4.5%, 7.4%, and 10.1% in the ninth decile (3.25–5.21) and 9.7%, 13.9%, and 18.0% in the tenth decile (RRI≥5.22) at 1, 3, and 5 years after LT, respectively. Table 4 shows examples of clinical characteristics of LT recipients with different RRI values and their corresponding 5-year cumulative incidences of post-LT ESRD. RRI for individual LT recipients can be calculated using the RRI calculator at https://rri.med.umich.edu.

RRI and Patient Survival

Figure 4 shows predicted patient survival by RRI decile. A dose-dependent decrease in patient survival was seen in each successive RRI decile (P<0.001). The 5-year post-transplant survival in the highest RRI decile was 58% compared with 76% for the reference patient. The median time to death after onset of ESRD was 4.3 years.

DISCUSSION

Post-transplant CRF and ESRD are major public health problems among all nonrenal solid organ transplant recipients.

Table 3. LT recipient characteristics by RRI decile

Median/Percent	RRI (*n*)								
	<0.59 (4394)	0.59–0.81 (4368)	0.82–1.00 (4270)	1.01–1.22 (4463)	1.23–1.48 (4315)	1.49–1.83 (4288)	1.84–2.35 (4338)	2.36–3.24 (4387)	3.25–5.21 (4348)	≥5.22 (4343)
Age at LT (yr)	47	52	53	54	54	55	55	55	55	55
African American	5.1%	4.7%	4.6%	5.1%	6.7%	9.1%	11.4%	13.1%	14.0%	17.6%
Cholestatic disease	40.0%	17.2%	9.3%	7.7%	5.6%	4.2%	4.6%	4.6%	4.5%	2.5%
Hepatitis C	12.3%	30.4%	42.4%	50.2%	51.4%	53.0%	51.4%	50.2%	46.0%	52.8%
BMI	24.8	26.5	26.9	27.5	27.6	28.0	28.0	28.1	28.2	28.6
Diabetes	1.2%	3.4%	4.9%	7.5%	11.4%	20.4%	30.6%	39.1%	45.2%	51.6%
Creatinine (mg/dl)	0.7	0.8	0.8	0.9	1.0	1.1	1.3	1.4	1.8	2.6
Bilirubin (mg/dl)	8.5	4.2	3.2	2.9	3.0	3.0	3.2	3.4	4.1	6.8
Albumin (g/dl)	3.0	3.0	3.0	2.9	2.9	2.9	2.9	2.8	2.8	2.8
Serum sodium (mEq/L)	135.0	136.0	136.0	137.0	137.0	136.0	136.0	137.0	136.0	137.0
Status-1	12.5%	4.7%	3.5%	2.8%	3.4%	2.9%	4.0%	5.6%	9.1%	8.1%
Previous LT	2.9%	3.0%	3.7%	4.1%	5.1%	5.7%	7.7%	8.9%	11.4%	18.8%
TIPSS	3.1%	5.0%	5.3%	6.4%	8.4%	9.0%	9.8%	10.3%	10.7%	13.6%
On acute dialysis at LT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	2.3%	12.3%	36.4%

Recipients of deceased donor LTs have the second highest cumulative incidence of post-LT CRF. ESRD is associated with increased morbidity and mortality in patients with a functioning nonrenal allograft.[2,5] This study describes the development and application of a method to quantify and prognosticate the risk of developing ESRD after deceased donor LT alone. Expressed as a risk score compared with a reference LT alone recipient, the RRI is an objective and validated tool based on a regression model with excellent performance characteristics that uses readily available recipient factors.

RRI describes the continuum of risk of ESRD among LT recipients and is applicable to all LT alone recipients, including those subjects receiving renal replacement therapy at LT. The trajectory of renal function over time reflects the duration of CKD. Therefore, we examined the effect of the slope of serum creatinine—from the time of listing to LT—on development of ESRD after LT. As previously shown, our current analysis also showed that a steep increase in serum creatinine (positive slope; representing an acute insult to kidneys as seen in patients with hepatorenal syndrome [HRS]) was associated with lower risk of post-LT ESRD.[5] However, based on the sensitivity analysis and practical limitation of not necessarily having all creatinine values at the time of LT to calculate RRI, the slope of creatinine was dropped from the final RRI model.

In addition to previously described risk factors of post-LT ESRD, our study also found a 28% increased risk of post-LT ESRD for LT recipients with a BMI$>$35 kg/m^2 compared with LT recipients with BMI$\leq$35 kg/m^2. High BMI is usually associated with metabolic syndrome and may serve as a surrogate for other comorbidities, such as hypertension and impaired fasting glucose, that may cause renal dysfunction over time.

Our study showed that certain factors were associated with a lower risk of ESRD. Patients with serum sodium$\leq$134 mEq/L at LT had a 31% lower risk of post-LT ESRD compared with those patients with serum sodium$>$134 mEq/L. Patients with hyponatremia are more likely to have HRS, and the majority of patients with HRS recovers renal function after LT alone.[10] This finding may explain the lower risk of post-LT ESRD associated with hyponatremia. Similarly, patients transplanted as status-1 also had a lower risk of post-LT ESRD compared with others. Approximately 10% of status-1 patients have concomitant AKI, which often resolves after LT alone. Finally, high bilirubin is commonly seen in patients with cholestatic liver disease. Cholestatic liver disease is infrequently associated with CKD, and therefore, it is not surprising that, after successful LT alone, such patients have a lower ESRD risk.

Under the current MELD-based donor liver allocation system, which accords substantial weight to serum creatinine, a large number of incremental incident post-transplant ESRD cases are being added to the overall ESRD population. These cases may be amenable to risk factor modification. Moreover, the ability of the RRI to identify those transplant candidates at highest risk may facilitate targeted focus on renal preservation. The 5-year cumulative incidence of post-LT ESRD is 1.1% in the first decile (RRI$<$0.59) and 1.5% in the second decile

(0.59≤RRI≤0.81). However, it increases to 10.1% in the ninth decile (3.25≤RRI≤5.21) and 18.0% in the tenth decile (RRI>5.21). The top two RRI deciles, which represented only 20% of recipients, contribute more than one half of the post-LT ESRD cases that are predicted to occur within 5 years of LT. In addition to a high burden of incremental morbidity and mortality, the annual estimated $87,561 cost of outpatient hemodialysis[11] will add markedly to the health care expenditures incurred to treat high RRI patients.

Knowledge of the future risk of ESRD may suggest ameliorative strategies for post-LT management and mitigate the post-LT ESRD risk. Risk stratification at the time of LT based on RRI coupled with stricter control of diabetes, stricter control of hypertension, weight loss strategies for obese patients, post-LT hepatitis C treatment using newer directly acting antiviral agents, and avoidance and/or minimization of renal insult during the perioperative period and post-LT follow-up by individualized tailoring of immunosuppression (*e.g.*, induction with biologic immunosuppressant agents with delayed introduction of CNI after LT or use of low-dose CNI with mycophenolate or mammalian target of rapamycin inhibitors, such as everolimus) may prevent or delay progression to ESRD, with salutary effects on patient survival.[12–14]

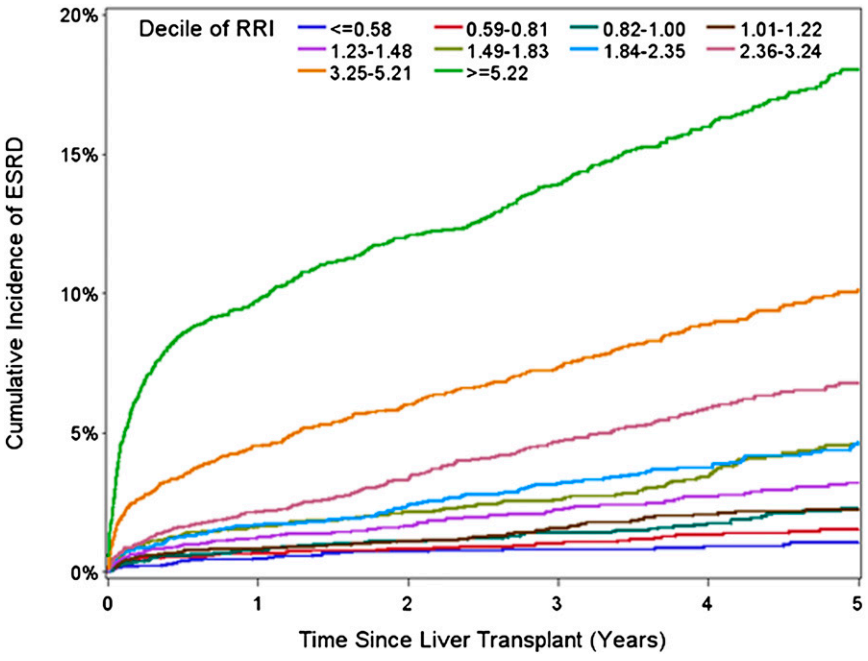

Figure 3. Cumulative incidence of post-LT ESRD stratified by RRI deciles. RRI deciles were based upon liver transplant recipient's characteristics at the time of transplant.

There are some limitations to this study that should be acknowledged. The observational study design results in potential bias because of patient selection and unmeasured patient characteristics. The simultaneous liver and kidney transplant (SLKT) incidence has increased significantly in the MELD era as an another unintended consequence.[15] Although the prognostic value of RRI cannot be extended to SLKT recipients, because such patients have already reached the ESRD end point by virtue of receiving a kidney transplant

Table 4. Examples of clinical characteristics of LT recipients with different RRI and corresponding 5-year post-LT ESRD cumulative incidence

RRI, Decile, Components	Patient 1	Patient 2	Patient 3	Patient 4
RRI[a]	1.0 (reference)	1.26	3.10	13.75
RRI decile	Third	Fifth	Eighth	Tenth
Age (yr)	53	53	53	53
African American	No	No	No	No
Cholestatic disease	No	No	No	No
Hepatitis C	No	No	No	No
Diabetes	No	No	Yes	Yes
BMI	30	30	30	30
Serum creatinine (mg/dl)	1.0	1.2	1.4	1.4
Serum bilirubin (mg/dl)	3.5	3.5	3.5	3.5
Serum albumin (g/dl)	2.9	2.9	2.9	2.9
Serum sodium (mMol/L)	140	140	140	140
Status-1	No	No	No	No
Previous LT	No	No	No	No
History of TIPSS	No	No	No	No
On acute dialysis pre-LT	No	No	No	Yes
5-yr post-LT ESRD cumulative incidence for decile	2.3%	3.2%	6.8%	18.0%

[a] $RRI = \exp^{[(0.00688\times(\text{recipient age}-53))+(0.4292 \text{ if African American})+(-0.3724 \text{ if cholestatic})+(0.2711 \text{ if HCV})+(0.7111 \text{ if diabetic})+(0.2450 \text{ if BMI}\geq 35)+(1.2521\times\ln(\text{creatinine}) \text{ if not on dialysis})+(-0.1525\times\ln(\text{bilirubin}/3.5))+(-0.3851\times\ln(\text{albumin}/2.9))+(-0.3706 \text{ if sodium}<134)+(-0.2671 \text{ if status-1})+(0.4359 \text{ if previous liver transplant})+(0.3129 \text{ if TIPSS})+(1.9097 \text{ if on dialysis})]}$

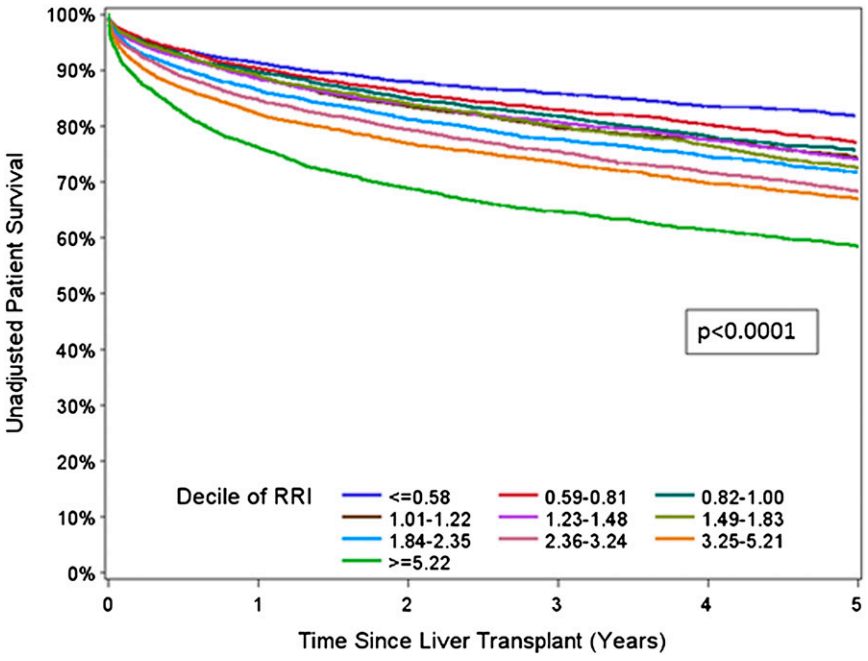

Figure 4. Unadjusted post-transplant patient survival stratified by RRI deciles. RRI deciles were based upon recipient's characteristics at the time of liver transplantation.

at LT, RRI may support decisions to perform LT alone among those patients who have some renal dysfunction but lower RRI.

In conclusion, RRI may serve as an important, objective, and validated risk measure to guide post-transplant patient management, individualized immunosuppression decision-making, and patient counseling. Patient-specific identification of ESRD risk using the RRI coupled with appropriately tailored management may prove to be valuable evidence-based tools for personalized medical intervention designed to reduce the risk of post-LT ESRD and improve patient survival among LT recipients.

CONCISE METHODS

Data Sources and Study Population

Our study was based on data obtained from the Scientific Registry of Transplant Recipients (SRTR). The SRTR maintains a database of all candidates for and recipients of solid organ transplants in the United States. Patients on waiting lists for organ transplantation and patients who receive organ transplants are followed on a periodic basis with the use of data collection forms completed by organ transplantation programs and submitted to the Organ Procurement and Transplantation Network. These follow-up data, in addition to data from the network regarding patients on waiting lists and the allocation of organs, are included in the SRTR database.

The SRTR supplements information submitted by organ transplantation programs with data matched at the subject level from the Centers for Medicare and Medicaid Services (CMS) and the Social Security Death Master File.[16] The Social Security Death Master File is used to augment information on vital status. CMS maintains a database of all patients treated for ESRD in the United States, which includes information about demographics, treatment, hospitalization, and costs for Medicare beneficiaries, and all other patients with ESRD who have received maintenance RRT. Data from the CMS ESRD program is used to supplement information on vital status and identify the initiation of chronic ESRD treatment (CMS 2728 Medical Evidence Form). This study was approved by the University of Michigan Institutional Review Board. A data use agreement was obtained from the SRTR for this project.

Our study population included recipients≥18 years of age at LT who had received deceased donor LT between February 28, 2002 and December 31, 2010 (n=43,514). Living donor and multiorgan transplants, including SLKT, were excluded. Recipients with evidence of ESRD (initiation of maintenance dialysis, placement on kidney waiting list, or receipt of a kidney transplant) before LT were also excluded from the analysis.

Analytical Approach

In the descriptive analysis, continuous variables were expressed as median and IQR; categorical variables were expressed as proportions. The primary outcome was new-onset post-LT ESRD, which was defined as the earliest of initiation of maintenance dialysis, waitlisting for kidney transplantation, or receipt of a kidney transplant. Patients were followed from the date of LT to the earliest of death or end of follow-up.[17] The incidence rate was calculated as the number of ESRD events divided by total patient time at risk expressed as patient-years.

Model Building

A Cox regression model was fitted to identify significant predictors of new-onset post-LT ESRD. Covariate selection was a nonautomated form of backward elimination. Specifically, we started the model-building process by fitting a model that contained every covariate suspected of affecting post-LT ESRD based on the previous studies. Those covariates with $P \leq 0.05$ were included in the final model. The following baseline covariates determined at the time of LT were included in model selection based on these data and previous studies:[2,5,18,19] recipient age, sex, race, diagnosis, BMI, status-1 (acute liver failure), pre-LT hypertension, diabetes mellitus, hospitalization status at LT, on life support at LT, on RRT at LT, previous LT, history of TIPSS, serum bilirubin, serum creatinine, slope of creatinine, acute dialysis, INR, serum sodium, and serum albumin.

Serum creatinine in a patient on dialysis is not meaningful. We parameterized creatinine and the dialysis by creatinine interaction and dropped the nonsignificant creatinine term that would apply to patients on dialysis. We also tested the interaction between serum creatinine and diabetes.

The slope of creatinine (from the time of listing to LT) was estimated using least square regression from all available creatinine values from the time of listing to LT. As previously shown, the slope of creatinine was significantly associated with ESRD ($P<0.001$). We performed a sensitivity analysis with and without the slope of creatinine, and it did not change the HR of other coefficients. We dropped the slope of creatinine from the final model, because all the creatinine values may not be available at the time of LT.

In addition, the model was adjusted for donor age, donor sex, cold ischemia time, local versus shared organ (regionally or nationally), and DCD.

The recipient and donor data on all the variables were nearly complete (0.05% or less missing), except for diabetes status (2.5% missing), TIPSS (4% missing), BMI (7% missing), cold ischemia time (8% missing), and serum sodium (28% missing). The mandatory submission of serum sodium along with MELD covariates went into effect November 1, 2004. Candidates listed and transplanted before November 1, 2004 accounted for the missing serum sodium data. For continuous variables, missing values were set to zero, and a missingness dummy variable was included in the model. This strategy is reasonable given that missing sodium was related directly to calendar year and did not depend on the event of interest or any of the remaining covariates. In addition, the missingness variable indicators for serum sodium and BMI were highly nonsignificant.

RRI

The RRI is a composite score comprised of the exponentiated sum of the patient-specific recipient factor parameter estimates from the adjusted Cox regression model. The RRI represents the relative risk of post-LT ESRD of an LT recipient with specific recipient characteristics compared with a reference recipient. The unadjusted cumulative probability of post-LT ESRD, stratified by deciles of RRI, was calculated using competing risk methods.[20]

Patient survival stratified by RRI decile was examined with Kaplan–Meier survival curves and compared using log-rank tests. All statistical analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC).

Model Validation

The IOC was used to estimate the goodness of fit for the models.[21,22] The IOC represents the percentage of pairs of subjects, where there is concordance between the predicted and observed ordering of outcomes. An IOC of 1.0 indicates perfect identification of the relative survival of 100% of all possible pairs of patients, whereas an IOC of 0.5 indicates that the model is no more predictive than chance (50%).[23] The IOC for a time-dependent Cox regression model is analogous to the C statistic computed from the area under the receiver operating characteristic curve for logistic regression models. The IOC and 95% confidence interval were computed for the entire study cohort. However, to evaluate a potential upward bias (overestimation) in the IOC from evaluating the model performance on the same dataset used to estimate parameters, we also computed the IOC for split datasets. The original cohort was randomly split into two equally sized training and validation datasets. The RRI model parameters were estimated based on the training dataset, and these estimates were then used with the validation dataset to compute the IOC. This procedure was performed 10 times on random cross-sections of validation cohort sets, and the mean IOC was computed.

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DISCLOSURES

None.

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