Donor Risk Index Predicts Graft Failure Reliably But Not Post-Transplant Infections

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Abstract

Background: The Donor Risk Index (DRI) is used to predict graft survival following liver transplantation, but has not been used to predict post-operative infections in graft recipients. We hypothesized that lower-quality grafts would result in more frequent infectious complications.

Methods: Using a prospectively collected infection data set, we matched liver transplant recipients (and the respective allograft DRI scores) with their specific post-transplant infectious complications. All transplant recipients were organized by DRI score and divided into groups with low-DRI and high-DRI scores.

Results: We identified 378 liver transplants, with 189 recipients each in the low-DRI and high-DRI groups. The mean DRI scores for the low- and high-DRI-score groups were 1.14 ± 0.01 and 1.74 ± 0.02 , respectively ($p < 0.0001$ for the difference). The mean Model for End-Stage Liver Disease (MELD) scores were 26.25 ± 0.53 and 24.76 ± 0.55 , respectively ($p = 0.052$), and the mean number of infectious complications per patient were 1.60 ± 0.19 and 1.94 ± 0.24 , respectively ($p = 0.26$). Logistic regression showed only length of hospital stay and a history of vascular disease as being associated independently with infection, with a trend toward significance for MELD score ($p = 0.13$).

Conclusion: We conclude that although DRI score predicts graft-liver survival, infectious complications depend more heavily on recipient factors.

BEFORE THE 1980s, the mortality associated with a post-operative infection following liver transplantation exceeded 50%. Over the subsequent two decades that rate decreased to 25% and then to less than 10%, respectively, with improved prevention, prophylaxis, recognition, and treatment of infections in this distinct patient population [1]. Today, infections continue to be a substantial cause of post-operative morbidity in liver transplant recipients despite improvements in survival rates. Infections are considered the most common life-threatening complication in chronically immunosuppressed recipients of solid organ transplants [2].

A number of risk factors have been identified for an increased risk of post-operative infection. Patient factors including diabetes mellitus (both through the effects of an increased concentration of HbA1c and perioperative hyperglycemia), nicotine use, and the systemic use of corticosteroids and other immunosuppressive medications may predispose to post-operative infection [3]. Malnutrition, mainly as protein deficiency, has also been associated with post-operative infection,

and a low serum albumin concentration has been identified as an independent risk factor for health care-associated infections in hospitalized cirrhotic patients [4]. Pre-operative microbial colonization, concurrent remote site infections, extremes of age, and obesity are other patient factors that increase the risk of post-operative infection [3].

Additional factors are believed to play a role in the increased frequency of infectious complications in liver transplant recipients specifically. Pre-transplant factors contributing to post-operative infection include chronic medical conditions, primary bacterial peritonitis, chronic biliary obstruction, and lengthy pre-operative hospitalization. A host of transplantation factors contribute to such infection, including the complexity of the surgical procedure, the prolonged duration of surgery, contamination of the operative site, transfusion requirements, and the frequency of subsequent operations for various complications (e.g., bleeding, anastomotic leak, graft failure) [1]. Post-operatively, liver transplant recipients, particularly those with poor initial graft function, have a longer recovery time,

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thereby enduring a longer exposure to health care-associated infections.

To help decision-making about the allocation of organs, specific donor characteristics have been identified as significant independent predictors of graft outcomes. These criteria were initially defined for kidney transplantation to decrease the discard rate of procured organs, and allowed identification of an "expanded donor group" of organs acceptable for transplantation [5]. This same concept has been applied to liver transplantation. The donor risk index (DRI) was created to predict quantitatively the risk of post-transplant graft failure in liver transplantation.

Seven donor factors and two procurement factors were incorporated into the DRI model to calculate a quantifiable DRI [6]. These factors include donor age, race, height, death from cerebrovascular accident (CVA), donation after cardiac death (DCD), cause of death classified as "other" (excluding trauma, CVA, or anoxia), split or partial graft, cold ischemia time, and location of organs based on donor service area [6]. These nine characteristics are incorporated into the DRI model to permit the use of a quantitative index to compare grafts, predict outcomes, and allocate organs ideally [6].

To date, the DRI has been used to predict graft survival following liver transplantation and to allow a quantifiable assessment of organ quality to assist in the matching and allocation of organs. We hypothesized that the DRI used to predict graft outcomes would also predict infectious complications in transplant recipients on the basis of the derangements of immunity known to occur with suboptimal early liver function.

Patients and Methods

This study was approved by the Institutional Review Board (IRB) for Health Sciences Research (HSR) at the University of Virginia (IRB-HSR #15576). The need for individual informed consent was waived because of the retrospective design of the study and the removal of donor- and recipient-identifying data.

We analyzed retrospectively all liver transplant recipients at our center from April 1, 2002 through September 30, 2009 and matched each recipient with the recipient's liver donor as identified within the United Network for Organ Sharing (UNOS) data base. Donor demographics evaluated included age, race, height, cause of death, and status of donation after cardiac death. We also identified donor operative variables including cold ischemia time, split or partial organ for transplantation, and region of donation. The DRI score was then calculated as described by Feng et al. for each liver donor [6]. The Model for End-Stage Liver Disease (MELD) score for each recipient was also calculated, using the current formula as defined by the United Network for Organ Sharing (UNOS) [7]. Each donor-recipient pair was characterized as having a DRI score in the lower (low DRI score) or upper (high DRI score) one-half of all patients receiving liver transplants, dividing the pairs into two groups of equal size. All liver transplant patients received standard prophylactic antibiotics peri-operatively (piperacillin-tazobactam) and our institution's standard immunosuppressive therapy post-operatively.

Patients generally received a tacrolimus-based immunosuppressive regimen, with blood concentrations of tacrolimus targeted at 5–10 mcg/mL. They also received corticosteroids at the time of transplantation, the dosages of which were then tapered over the first 6 mo after transplantation. Mycophen-

olate mofetil was added to patients' regimens after any episode of donor-organ rejection. Antibody induction, primarily done with antibodies to CD25, was used in patients with poor renal function at the time of transplantation, to delay the administration of tacrolimus.

A prospectively collected data set tracking infectious complications of all in-patient liver transplantation patients was used to identify post-transplant infections in our study population. During the study period, data were collected prospectively through a thrice-weekly chart review, patient examination, and review of electronic laboratory, microbiology, and pharmacy reports. From this prospective data set we recorded age, gender, race, co-morbidities, isolated micro-organisms, antibiotic treatments, patient location at the time of onset of the infection, and various outcomes of liver-transplant recipients (i.e., post-operative length of stay). Infections were defined in accordance with the definitions and diagnostic criteria of the U.S. Centers for Disease Control and Prevention [8]. All recorded episodes of infection were those occurring post-operatively and within the first year following transplantation.

The mean DRI score, number of infectious complications, and MELD score were identified for the low- and high-DRI-score groups. Demographics and outcomes were tabulated and reported for each DRI group. Statistical analyses were done with SAS Statistical Analysis Software version 9.1.3 (SAS Institute, Cary, NC). We used χ^2 -square analysis or the Fisher exact test, as appropriate, to compare categorical variables in the low- and high-DRI-score groups, with comparison of continuous variables done with the Student *t*-test. A value of $p < 0.05$ was considered statistically significant. A multiple logistic regression analysis was done to determine independent predictors of post-operative infection, including variables selected a priori. We selected the following variables for inclusion in the model: Age, gender, MELD score, diabetes mellitus, coronary artery disease, renal dysfunction (serum creatinine concentration ≥ 2.0 mg/dL), pulmonary disease (active medications for pre-admission lung disease), peripheral vascular disease, and DRI score analyzed as both a continuous and dichotomous ("high" or "low" about the median) variable. From this multivariable model, we determined odds ratios (ORs).

Results

Our center performed a total of 378 liver transplants from April 1, 2002 through September 30, 2009. These were divided into low- and high-DRI-score groups consisting of 189 liver transplant recipients in each group (Table 1), with the overall median DRI score being 1.36. The mean DRI scores for the low- and high-DRI-score groups were 1.14 ± 0.01 and 1.74 ± 0.02 , respectively ($p < 0.0001$ for the difference). Although the mean numbers of infectious complications per patient were 1.60 ± 0.19 in the low- and 1.94 ± 0.24 in the high-DRI-score groups, respectively, and the two groups' mean lengths of stay were 17.1 ± 1.2 d and 16.4 ± 1.1 d, respectively, the MELD and DRI scores in the two groups were not significantly associated with one another.

Donor demographics

Donor demographics were compared after the liver transplant donors were divided into the low- and high-DRI-score groups in the study. Table 2 shows the demographics of each group separately and a comparison of the differences between

TABLE 1. DONOR RISK INDEX AND MODEL FOR END-STAGE LIVER DISEASE SCORES, INFECTIONS PER PATIENT, AND HOSPITAL LENGTH OF STAY IN LOW- AND HIGH-DONOR RISK INDEX-SCORE GROUPS

	All patients	Low DRI	High DRI	p value
Number of patients	378	189	189	
DRI score	1.44±0.02	1.14±0.01	1.74±0.02	0.0001
MELD score	25.51±0.38	26.25±0.53	24.76±0.55	0.052
Infections	1.77±0.15	1.60±0.19	1.94±0.24	0.26
Mean length of stay (days)	16.8 ±0.8	17.1 ±1.2	16.4 ±1.1	0.69

DRI=Donor Risk Index; MELD=Model for End-Stage Liver Disease.

the two groups. Donors in the low-DRI-score group were younger and taller, and were more likely to be white, victims of trauma, to be standard donors, and to have their livers procured locally.

Infectious complications

A total of 673 infectious complications, in 378 patients, occurred during the study period, with an overall mean of 1.8±0.15 infections per patient. Numerically more infections occurred in the high- (371) than in the low-DRI-score group (302), but this difference did not reach statistical significance ($p=0.26$) as seen in Table 3. In both DRI-score groups the abdomen was the most common site of infection, followed by the blood stream, urine, lungs, and surgical incision. The organism isolated most commonly in both groups was vancomycin-resistant *Enterococcus faecium* (VRE). Each group had an approximately equal frequency of isolation of *Clostridium difficile*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *E. faecium* (non-VRE). The high-DRI-score group had significantly more frequent isolation of *Candida glabrata* and *Escherichia coli* than did the low-DRI-score group.

The patient location at the time of infection was significantly different for the two DRI-score groups, and reflects the timing of infection. The high DRI-score group had significantly more frequent infections in the intensive care unit (ICU) than did the low DRI group (39% vs. 27%, respectively

$p=0.002$), whereas the low DRI-score group had more frequent infections at home following discharge from the hospital (32% vs. 22%, respectively, $p=0.004$).

The logistic regression model predicting infection (c statistic=0.791) revealed only length of stay (OR 1.09, 95% CI 1.05–1.12) and peripheral vascular disease (OR 4.34, 95% CI 1.30–14.50) as independent predictors of post-operative infections (Table 4). Age, sex, MELD score, diabetes mellitus, coronary artery disease, renal dysfunction, pulmonary disease, and DRI score were not predictive of infection following liver transplantation.

Discussion

Post-operative infections, and particularly surgical site infections (SSI), in the population undergoing liver transplantation have a dramatic impact on graft and patient survival as well as resource utilization. Liver transplant recipients have historically had a markedly higher rate of infection, including SSI, than any other solid organ transplant recipients or general surgical patients [1,9–10]. Prolonged operative time, surgical complexity, risk of gastrointestinal contamination, immunosuppression, metabolic derangements, and the compromised ability of the immunosuppressed host to clear residual bacterial contamination all make liver transplant recipients particularly susceptible to infection [1–2].

TABLE 2. DONOR DEMOGRAPHICS FOR LOW- AND HIGH-DONOR RISK INDEX-SCORE GROUPS

	Low DRI	High DRI	p value
Donor age (years) mean (range)	32.2±0.9, (11–59)	51.0±1.1, (11–79)	<0.0001
Donor race N (%)			
White	157 (83.1%)	118 (62.4%)	<0.0001
Black	27 (14.3%)	64 (33.9%)	<0.0001
Other	5 (2.7%)	7 (3.7%)	=0.34
Donor height (cm) mean (range)	176.0±0.7, (147–213)	168.5±0.8, (130–193)	<0.0001
Donor cause of death N (%)			
Trauma	126 (66.7%)	29 (15.3%)	<0.0001
CVA	34 (18.0%)	130 (68.8%)	<0.0001
Anoxia	25 (13.2%)	23 (12.2%)	=0.88
Other	4 (2.1%)	7 (3.7%)	=0.54
Donation after cardiac death N (%)	1 (0.5%)	9 (4.8%)	=0.02
Split/partial transplant N (%)	0	5 (2.6%)	=0.06
Cold ischemia time (hours) mean (range)	9.3±0.2, (2–20)	10.0±0.3, (3.3–30)	=0.04
Donation region N (%)			
Local	140 (74.1%)	101 (53.4%)	<0.0001
Regional	47 (24.9%)	84 (44.4%)	<0.0001
National	2 (1.1%)	4 (2.1%)	=0.69
Average DRI score	1.14±0.01	1.74±0.02	<0.0001

CVA=cerebrovascular accident; DRI=Donor Risk Index.

TABLE 3. INFECTIOUS OUTCOMES FOR DONOR RISK INDEX-SCORE GROUPS

	Low DRI	High DRI	p value
Total number of infections	302	371	
Infections per patient (N)	1.60±0.19	1.94±0.24	0.26
Site of infection N (% of infections)			
Abdomen	80 (26%)	98 (26%)	1.00
Blood stream	53 (18%)	77 (21%)	0.33
Urine	52 (17%)	53 (14%)	0.34
Lung	32 (11%)	50 (13%)	0.29
Surgical site, incisional	20 (7%)	30 (8%)	0.56
Organisms isolated N (% of isolates)			
VRE	42 (14%)	53 (13%)	0.91
<i>Clostridium difficile</i>	20 (7%)	26 (6%)	0.76
<i>Klebsiella pneumoniae</i>	19 (6%)	30 (7%)	0.46
<i>Pseudomonas aeruginosa</i>	16 (5%)	18 (4%)	0.86
<i>Enterococcus faecium</i> (non-VRE)	16 (5%)	21 (5%)	0.87
<i>Escherichia coli</i>	10 (3%)	28 (7%)	0.02
<i>Candida glabrata</i>	15 (5%)	38 (9%)	0.01
Location at time of infection N (%)			
Intensive care unit	80 (27%)	140 (39%)	0.002
Surgical ward	123 (41%)	139 (39%)	0.43
Home	96 (32%)	81 (22%)	0.004

VRE=vancomycin-resistant *Enterococcus*.

Surgical site infections (SSIs) in particular impose a marked economic burden and represent a substantial clinical problem. It has been shown that SSI in liver transplant recipients is associated with a prolonged stay in the ICU and extends these patients' hospital stays by approximately one week [9]. Similarly, patients with SSI following liver transplantation utilize more resources and accrue at least \$2,000–\$4,000 in additional hospital cost [9,11–12]. Beyond this, SSIs have been associated with a significant increase in graft loss and patient mortality within the first year following transplantation (RR 3.06, 95% CI 1.66–5.64; $p < 0.001$) [10]. It is clear that post-operative infections in liver transplant recipients are a substantial burden, and an attempt should be made to predict and prevent these complications.

Post-operative infections are the consequence of a complex interaction among intrinsic host status, organ quality, and environmental factors, making it extremely difficult to predict

their occurrence in the unique population of patients undergoing liver transplantation. Many models have been developed and validated to predict outcomes before and after organ transplantation, as in the case of the MELD score, which predicts mortality during the period of waiting for liver transplantation, as well as patient and graft survival, and is currently the scale used for allocating liver transplants in the United States [13–15]. The DRI is an index of organ quality predicting graft failure and mortality as outcomes of liver transplantation; however, neither it nor any other model or index has proved to be a good predictor of infectious complications [13,14]. As our logistic regression model reveals, DRI score (analyzed as either a continuous or dichotomous variable) does not appear to be an independent predictor of post-operative infection in liver transplant recipients.

It was our hypothesis that a transplant liver of lower quality, with an associated higher DRI score, would cause

TABLE 4. LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS ASSOCIATED WITH INFECTION FOLLOWING KIDNEY TRANSPLANTATION

Predictor	Wald χ^2	Odds ratio	95% CI	p value
Length of stay	28.55	1.09	1.05– 1.12*	<0.0001
Peripheral vascular disease	5.70	4.34	1.30–14.50*	0.02
MELD score	2.20	1.03	0.99– 1.06	0.13
Reoperation	1.39	1.41	0.80– 2.51	0.24
Coronary artery disease	0.31	0.76	0.28– 2.03	0.58
Diabetes mellitus	0.15	1.10	0.67– 1.83	0.70
Donor Risk Index score (continuous) [†]	0.11	1.12	0.59– 2.10	0.74
Pulmonary disease	0.08	0.89	0.40– 2.00	0.78
Renal dysfunction	0.01	1.04	0.53– 2.06	0.90
Age	0.01	1.00	0.97– 1.03	0.95
Sex	0.002	0.99	0.58– 1.69	0.97

*Independent predictors of infection.

[†]Donor Risk Index score as dichotomous variable similarly a non-significant predictor (OR 1.03, 95%CI 0.65–1.64). c statistic=0.791.

MELD=Model for End-Stage Liver Disease.

more post-operative infectious complications in its recipient than one of average or higher quality. We presumed that organs of poorer quality would be associated with poorer early function, a need for additional interventions, and increased ICU and hospital stays, all contributing to an increased risk of infection. The high-DRI-score group in our study did have more frequent infectious complications than the low-DRI-score group (371 vs. 302 infections, respectively), but this did not reach significance ($p=0.26$). Our data imply that the frequency of infectious complications of liver transplantation may be determined more strongly by recipient factors and less by donor factors than hypothesized, particularly when the donor's specific infectious diseases history is unknown.

In terms of the distribution of infections in our study by location and type of pathogen, there was no difference between the low- and high-DRI-score groups. In both groups the abdomen was the most common site of infection, followed by the blood stream and urinary tract. The five most common organisms isolated were the same in both the low- and high-DRI-score groups except for a higher rate of *C. glabrata* infection in the high-DRI-score group. These data are consistent with current reports of infections following liver transplantation, and also do not appear to be influenced by donor factors.

The times of occurrence of infections was significantly different in the low- and high-DRI-score groups in our study; this was probably related to the promptness of graft function. The high-DRI-score group had more infectious complications in the ICU (early in the post-operative period), whereas the low-DRI-score group had more frequent complications at home. This supports our hypothesis that a high DRI score, indicating an organ of lower quality with associated poor early graft function, may not be able to overcome a bacterial burden initially, resulting in early infection. Even though the overall rates of infection were not different in the groups with low- and high-DRI-scores in our study, the association of organs with high-DRI-scores with more early, ICU-acquired infections suggests some possible changes in practice. Thus, for example, patients receiving livers with high DRI scores might need more intense surveillance for infection or a more aggressive approach toward starting the administration of empiric antibiotics than might recipients of organs with low DRI scores. Whether or not these changes could improve long-term outcomes awaits further study.

Immeasurable multifaceted interactions between the host's immune system and the functionality of a donor liver make it nearly impossible to predict infectious complications on the basis of a single organ or single recipient characteristic. However, donor characteristics, as quantified by the DRI, do not appear to affect infectious outcomes in liver transplant recipients.

Author Disclosure Statement

No competing financial interests exist.

References

1. Winston DJ, Emmanouilides C, Busuttil RW. Infections in liver transplant recipients. *Clin Infect Dis* 1995;21:1077–1091.
2. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357:2601–2614.
3. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999;20:24–280.
4. Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. *Am J Gastroenterol* 1999;94:2193–2197.
5. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: An approach to expanding the pool of kidney donors. *Transplantation* 2002;74:1281–1286.
6. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: The concept of a donor risk index. *Am J Transplant* 2006;6:783–790.
7. United Network for Organ Sharing. 28 January 2009. www.unos.org/docs/MELD_PELD_Calculator_Documentation.pdf. (Last Accessed 14 January 2011).
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.
9. Prado MEG, Matia EC, Ciuro FP, et al. Surgical site infection in liver transplant recipients: Impact on the type of perioperative prophylaxis. *Transplantation* 2008;85:1849–1854.
10. Hellinger WC, Crook JE, Heckman MG, et al. Surgical site infection after liver transplantation: Risk factors and association with graft loss or death. *Transplantation* 2009;87:1387–1393.
11. Kirkland KB, Briggs JP, Trivette SL, et al. The impact of surgical-site infections in the 1990s: Attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol* 1999;20:725–730.
12. Hollenbeak CS, Alfrey EJ, Souba WW. The effect of surgical site infections on outcomes and resource utilization after liver transplantation. *Surgery* 2001;130:338–395.
13. Bonney GK, Aldersley MA, Asthana S, et al. Donor risk index and MELD interactions in predicting long-term graft survival: A single-centre experience. *Transplant Proc* 2009; 87:1858–1863.
14. Manduca Palmiero HO, Kajikawa P, Boin IFSF, et al. Liver recipient survival rate before and after model for end-stage liver disease implementation and use of donor risk index. *Transplant Proc* 2010;42:4113–4115.
15. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: Application of survival models to liver allocation. *Liver Transpl* 2001;7:567–580.

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