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Donor biomarkers as predictors of organ use and recipient survival after neurologically deceased donor organ transplantation

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Abstract

Purpose—We sought to build prediction models for organ transplantation and recipient survival using both biomarkers and clinical information.

Materials and Methods—We abstracted clinical variables from a previous randomized trial (n=556) of donor management. In a subset of donors (n=97), we measured two candidate biomarkers in plasma at enrollment and just prior to explantation.

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Declarations of Interest

None

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Results—Secretory leukocyte protease inhibitor (SLPI) was significant for predicting liver transplantation (C-statistic 0.65 (0.53, 0.78)). SLPI also significantly improved the predictive performance of a clinical model for liver transplantation (integrated discrimination improvement (IDI): 0.090 (0.009, 0.210)). For other organs, clinical variables alone had strong predictive ability (C-statistic >0.80). Recipient 3-years survival was 80.0% (71.9%, 87.0%). Donor IL-6 was significantly associated with recipient 3-years survival (adjusted Hazard Ratio (95% CI): 1.26(1.08, 1.48), $P = 0.004$). Neither clinical variables nor biomarkers showed strong predictive ability for 3-year recipient survival.

Conclusions—Plasma biomarkers in neurologically deceased donors were associated with organ use. SLPI enhanced prediction within a liver transplantation model, whereas IL-6 before transplantation was significantly associated with recipient 3-year survival.

Keywords

Organ donation; biomarker; clinical trial; transplantation; risk prediction; brain death

Introduction

On average, 22 people in the United States (US) die every day from the lack of available organs for transplantation [1]. The number of patients on waiting lists far exceeds the number of organ donors that become available. Moreover, the number of organs used per donor has remained relatively constant over time [2]. This situation necessitates the use of organs from less optimal donors [3]. Despite efforts to increase organ donation, there remains a critical shortage in both organ donors and organ procurement. Thus, more specific methods to discriminate low-risk from high-risk organs are needed.

Donation after neurologic death (DND) remains the major source of solid organs for transplantation [4]. DND is associated with increased systemic inflammatory response from incompletely known mechanisms [4-6]. IL-6 is a pleiotropic cytokine, and takes part in innate and adaptive immunity. Previous studies have demonstrated that IL-6 is associated with both acute [7, 8] and chronic rejection [9-11] in organ transplantation. Anti-IL-6 has been investigated as a potential therapy for antibody-mediated rejection [10, 12]. Moreover, elevated plasma IL-6 concentrations in the donor are associated with prolonged hospitalization time in recipients [13] as well as delayed graft function [14]. We previously found that higher levels of plasma IL-6, when measured in the donor prior to transplantation, were associated with decreased hospital free survival in transplant recipients [15]. SLPI, a small (12 kDa) nonglycosylated cationic protein, is synthesized by epithelial cells as well as inflammatory cells [16]. Apart from its well-known role in inhibiting proteolytic enzyme activities, SLPI also has direct anti-inflammatory effects by reducing pro-inflammatory cytokine production [16]. A recent study also demonstrated that SLPI uptake by the donor liver during perfusion is associated with graft injury [17]. Studies have shown that biomarkers in recipients predicted short-term outcomes in liver transplantation [18, 19]. Donor age as well as other clinical characters, such as hypertension, were also found to be associated with worse outcomes in recipients [20, 21]. Thus, the efficiency of transplantation may partially depend on both inflammatory cytokines and clinical characteristics of donors.

Accordingly, the aim of this study was to build risk-prediction models for organ transplantation and organ recipient survival using both clinical information and biomarkers (IL-6 and SLPI) in the donors.

Materials and Methods

The study was a planned analysis of clinical and biomarker data collected from donors enrolled in the Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) Study, and used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractor. Detailed study methods have been published previously [22, 23]. In brief, neurologically deceased organ donors were enrolled from eight organ procurement organizations (OPOs) in the US between October 2009 and March 2013. The trial was approved by each participating OPO scientific committee and by the University of Pittsburgh Committee for Oversight of Research and Clinical Training Involving Decedents (CORID). Excluding criteria included: donors who were less than 16 years old or receiving extracorporeal membrane oxygenation or ventricular assist device support, who had severe aortic regurgitation, intracardiac shunt or were on an intra-aortic balloon pump, who could not be performed with minimally invasive haemodynamic monitoring with a lithium dilution cardiac output (LiDCO) device, who received lithium therapy before brain death, who were previously enrolled in an experimental protocol in which cytokines were the therapeutic targets, who had received chemotherapy or any other condition resulted in leucopenia, who had received anti-leukocyte drugs and those donors who were deemed unsuitable for organ donation by the OPO. Complete clinical data were available from 505 donors. Participation in this substudy was optional and only four of the enrolling sites from the parent trial participated. From four clinical sites, we collected plasma for biomarker analysis (n=120). There were 23 donors aborted or with missing data. Our final organ donor dataset was composed of donors containing both complete clinical and biomarker information (n=97) (Figure 1). Data from organ recipients were collected from 266 patients whose organs were donated by 86 organ donors. The remaining 11 donors did not have any organs used.

Biomarker Assays

Blood was collected from donors at enrollment and before transfer to the operating room for ex-plantation. These samples were processed at the site and separated plasma was frozen and shipped on dry ice to the CRISMA laboratory where it was stored at -80°C until used for biomarker assays. Samples were thawed and assayed for IL-6 and SLPI in batches. IL-6 was measured using the Meso Scale Discovery (Rockville, MD) Kit and SLPI using the R&D Systems (Minneapolis, MN) Kit according to manufacture instructions. Technicians were blinded to all clinical information.

Statistical analysis

Our co-primary outcomes were total number of organs transplanted per donor and recipient 3-year survival. Secondary outcomes were use of each organ type and 6 month hospital free survival (6mHFS). Since the biological ranges of both biomarkers are very large, log transformation was conducted on biomarker values before all model fittings. First, for number of organs transplanted and use of each organ, 3 sets of models were fit: multivariable logistic regression with clinical variables only; multivariable logistic regression with biomarker variable only; and multivariable logistic regression with both clinical variables and biomarker variables. Bootstrap *C*-statistic was used to obtain prediction performance of all the models due to the lack of an external validation dataset. Prediction improvement of adding biomarkers to clinical models was assessed by Bootstrap IDI and differences in *C*-statistics[24]. Second, Kaplan-Meier estimates were used to estimate 3-year recipient survival. In addition, a multivariable Cox proportional hazards model was built for recipient 3-years survival. The same method was used to identify biomarker that could improve clinical model prediction performance. Univariable Cox regression models were built to evaluate association between biomarker and 6mHFS. Finally, we built a frailty model[25] for 3-year survival of kidney recipients using biomarker variables only. A $P < 0.05$ or confidence interval without containing 0 (for IDI) was considered statistically significant. All analyses were conducted using SAS 9.4 (Cary, NC) and R 3.2.2 (URL: <https://www.r-project.org/>).

Results

Characteristics of donors are shown in Table 1. Mean donor age was 43.8 years old and 11.3% of patients had a history of diabetes, and 38.1% had a history of hypertension. Expanded criteria was met by 26.8% of donors. Of the 97 donors in our final analysis cohort, most donated kidneys and livers (80.4% and 74.2%, respectively) (Table 2a). Almost half (48.5%) of the donors had greater than 3 organs used for transplantation (Table 2b).

Predicting organ use

The best-performing clinical models for total number of organs transplanted and for each individual organ are shown in Table 3. Donor age was a dominant variable because it is used as the primary selection criterion for all organs. For all organs together, only history of hypertension added to age in the final clinical model. Other variables, along with age, were predictive for individual organs (Table 3). Clinical models showed good discrimination effect for each organ (excluding lung) as well as total numbers of organs transplanted (*C*-statistic > 0.80) (Supplementary Table 1). SLPI at both enrollment and just prior to explantation had modest predictive ability (*C*-statistic 0.65) for liver transplantation but not for other organs (Table 4). When combined with clinical variables, pre-explantation SLPI was associated with reduced odds of use of the liver (adjusted OR (95% CI): 0.13 (0.03, 0.70), $P=0.02$) and improved the *C*-statistic from 0.80 (0.69, 0.89) to 0.85 (0.76, 0.92) for predicting use of the liver (*C*-statistic difference 0.051 (−0.011, 0.113)) (Supplementary Table 2). Furthermore, IDI for pre-explantation SLPI versus clinical variables alone was 0.090 (0.009, 0.210), which indicates significant improvement. There was no significant

improvement in discrimination when SLPI was added to clinical models for any other organs, nor was IL-6 predicative alone or in combination for use of any organs.

Predicting recipient survival

Kaplan-Meier survival estimates for recipients ($n=266$) at 3 years was 80.0% (95% CI: 71.9-87.0%), (Supplementary Figure 1). Characteristics of recipients are shown in Supplementary Table 3. Pre-explanation IL-6 was associated with an increased hazard (adjusted HR (95% CI): 1.26 (1.08, 1.48), $P=0.004$). “Expanded criteria” [26] was the only clinical variable that appeared to influence recipient survival ($P=0.007$) in the full Cox proportional hazards model. However, the predictive ability of this model was poor (C -statistic 0.59 (0.49, 0.69)). Neither IL-6 nor SLPI performed well (alone or together) for predicting 3-year survival (Table 5); although pre-explanation IL-6 (C -statistic 0.56 (0.44, 0.68)) achieved a C -statistic similar to the clinical model. Moreover, when pre-explanation IL-6 was combined with expanded criteria, the C -statistic improved to 0.64 (0.50, 0.79) (Table 5). However, neither IDI (−0.002 (−0.08, 0.13)) nor the difference in the C -statistic (0.05 (−0.04, 0.14)) was significant (Supplementary Table 4). Neither IL-6 nor SLPI were significant predictors of 6mHFS (data not shown). Finally, since a kidney from one donor could be provided to two recipients, we assessed kidney recipient 3-year survival using a frailty model to account for this potential correlation. Among age, race, blood type, gender, history of diabetes, history of hypertension and expanded criteria, history of diabetes was the only clinical variable that predicted survival in this case, which showed weak predicting influence (C -statistic 0.5). When we assessed the predictive effect of biomarkers, neither of them demonstrated strong predictive effects (Supplementary Table 5), but again pre-explanation IL-6 had the strongest C -statistic (0.66, $P=0.05$). We did not evaluate lung recipients this way given the small sample size ($n=28$). Enrollment and pre-explantation SLPI and IL-6 are shown in Supplementary Table 6. Finally, there was no difference between protocolized care group and standard care group for the two biomarkers before transplantation (Supplementary Table 7).

Discussion

In this study, we validated a previously reported [15] association between increased pre-explantation plasma IL-6 in the donor and decreased survival in the recipient. We also describe a new association between a novel biomarker, SLPI, measured in the neurologically deceased donor, and the usability of the liver.

IL-6 is an important cytokine taking part in host defense and produced response to various stimuli [27]. There are two different types of IL-6 receptors, soluble receptor (sIL-6R) and membrane receptor (IL-6R). IL-6R is mainly expressed on hepatocytes, neutrophils, monocytes and CD4+ T cells [28, 29]. The major effects of IL-6 include promoting synthesis of a series of acute phase proteins (like C reactive protein, serum amyloid A, fibrinogen), hematopoiesis by interrupting iron and zinc transporter function and promoting mature of megakaryocyte. It also connects innate immune response with adaptive immune response by upregulating ratio of Th17/Tregs and promoting activated B cells to differentiate into Ab-producing plasma cells [27]. Dysregulated IL-6 expression is associated with

autoimmune diseases and chronic inflammatory diseases [27-29]. The importance of IL-6 in transplantation has been identified in prior studies. Both IL-6 and its receptor system were activated in donor hearts [30], and levels of IL-6 were related to donor heart use [31]. The mechanism for IL-6-associated donor heart dysfunction might be the JAK2-STAT3-iNOS signaling pathway [32]. In liver transplantation, elevated plasma concentrations of IL-6 in donors before transplantation was associated with increased postoperative complications [18] IL-6 expression in donor lungs was related to bronchiolitis obliterans syndrome [33] and primary graft dysfunction [34].

In present study, IL-6 before transplantation was associated with recipients' 3-year survival, with HR = 1.26 (1.08, 1.48), $P = 0.004$. However, converting the association between donor IL-6 and recipient survival into a clinical test will be difficult. IL-6 failed to discriminate well, exhibiting only weak predictive ability (C-statistic 0.56). Although IL-6 was as informative as extended donor criteria and we found no other clinical variables that increased the performance of this model, IL-6 showed only modest improvement in predictive value of the model using just expanded donor criteria (C-statistic increased from 0.59 to 0.65).

The effect of donor age on recipient outcome appears to be complex. Because age is associated with risk for cardiovascular disease and other comorbidities, it is a prime variable for clinical decision making and is included in expanded criteria for organ transplantation [35, 36]. But the roles of donor age in recipient survival in different studies were not consistent. Three studies [37-39] on liver transplantation and two studies [40, 41] on heart transplantation demonstrated that donor age was not an independent hazard factor for recipient survival. Among these five studies, two studies [38, 41] set the cut off for advanced age at 60 years and 55 years, while remaining [37, 39, 40] used a cut off of 50 years. Moreover, in the studies which showed donor age as a hazard [42, 43], the HR for donor age was very close to 1, or they selected an older age for the cut off. Donor mean age in our population was 43.8 years old, which was relatively young among these studies, and this may partially explain the strong role of donor age in our study. Another potential reason may be that organ selection criteria has become more mature compared to around 10 years ago. As mentioned previously [37], donors are not usually declined according to age alone. If organs from old donors could be selected properly, it would largely extend donor pool. Survival was also influenced by recipient characteristics, including time on the waiting list. These considerations motivate the use of organs from older donors [44].

A more promising candidate as a predictive marker is SLPI. SLPI is well known for its inhibition of serine proteases, like neutrophil elastase (NE), cathepsin G and protease 3 [16]. SLPI also competes with NF-KB-p65 for binding to promoter regions of pro-inflammatory genes to inhibit NF-KB activity [45]. It is also an antimicrobial agent partially because of its cationic nature and ability to perforate bacteria membranes [46]. SLPI also regulates tumor cell growth [47], and plays an important role in differentiation, proliferation and survival in neural stem cells [16]. So far, SLPI has been considered a therapeutic candidate in lung diseases [16], a biomarker in some cancer [47] and as a potential antimicrobial agent. The role of SLPI in organ transplantation is less understood. One study demonstrated that in liver transplantation, SLPI uptake within the graft during perfusion was negatively associated

with postoperative function [17]. Also in cardiac transplantation, SLPI played a vital role in early myocardial perfusion and post-ischemic inflammation [49]. In our study, increased plasma SLPI in the donor was associated with reduced use of livers and added information to a full clinical model. This is actually quite surprising because the use of the liver is mainly determined by the clinical variables in the model (age, expanded criteria and liver function tests) and SLPI appears to therefore capture some other aspect of clinical judgement. Why this relationship is specific to the liver is unclear.

Indeed, clinical factors alone predicted organ use for transplantation well. This is not surprising because clinical variables are used in assessing which organs are accepted. Age was the common predictor for all the organs used for transplantation as well as the total number of organs transplanted per donor, which is consistent with prior studies [15, 20, 50, 51]. Nevertheless, the addition of SLPI to a clinical model improved model performance by IDI for the liver (although the improvement in the C-statistic from 0.8 to 0.85 was not significant).

Our study has several limitations. First, it is an observational study with relatively small sample size. Like all observational studies, we cannot infer causality between risk factors and outcomes, and cannot exclude residual confounding variables despite the detailed characteristic of donor and recipient. Second, the lack of unified objective criteria for donor management may lead to variation in practice across centers. Even though, it is difficult to control the donor management, OPO staffs as well as transplant surgeons were blind to the biomarkers, thus care decisions were not influenced by these results. Third, post-operative complications, may also have confounded our survival analysis. Forth, since the current study used data from a randomized trial, we may have standardized practice more than is usual in the routine care of DND donors.

Conclusions

In conclusion, we have validated an association between donor plasma IL-6 and 3-year recipient survival. However, even when added to extended donor criteria the predictive value of IL-6 is only modest. Plasma SLPI concentrations in the donor prior to explantation had significant prediction performance alone and could enhance the predictive value of clinical variables for predicting use of livers. This is a novel finding and will require confirmation in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

IL-6	interleukin-6
SLPI	secretory leukocyte protease inhibitor
IDI	integrated discrimination improvement
DND	donation after neurologic death
MOOnIToR	Monitoring Organ Donors to Improve Transplantation Results
SRTR	Scientific Registry of Transplant Recipients
OPTN	Organ Procurement and Transplantation Network
HRSA	Health Resources and Services Administration
OPOs	organ procurement organizations
CORID	Committee for Oversight of Research and Clinical Training Involving Decedents
OR	odds ratio
HR	hazard ratio

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Highlights

- Selection criteria for organs from neurologically deceased donors are imperfect
- SLPI was significant for predicting liver transplantation
- SLPI also improved prediction of a clinical model for liver transplantation
- Clinical variables alone had strong predictive ability for other organs
- Donor IL-6 was significantly associated with recipient 3-years survival
- Neither clinical variables nor biomarkers had strong prediction for 3-yr survival

Figure 1. Study flow and cohort selection.

Out of 556 neurologically deceased organ donors, 505 donors had complete clinical data. From four clinical data sites, we collected plasma analysis (n=120). After excluding missing or aborted data (n=23), 97 donors containing both complete clinical and biomarker information were included in our final data set.

Table 1.

Characteristics of donors

Donor Characteristics (n=97)	
Age (years)	43.8 (15.1)
Race	
White	86 (88.7%)
Black or African American	6 (6.2%)
Others	5 (5.1%)
Blood Type	
A: A	20 (20.6%)
A1: A1	12 (12.4%)
A1B: A1B	1 (1.0%)
A2: A2	2 (2.1%)
A2B: A2B	0
AB: AB	1 (1.0%)
B: B	10 (10.3%)
O: O	51 (52.6%)
Gender	
Female	47 (48.5%)
Male	50 (51.5%)
History of Diabetes (Yes)	11 (11.3%)
History of Diabetes	
No	86 (88.7%)
YES, 0-5 Years	5 (5.1%)
YES, 6-10 Years	2 (2.1%)
YES, >10 Years	4 (4.1%)
YES, Duration Unknown	0
History of Hypertension (Yes)	37 (38.1%)
History of Hypertension	
No	60 (61.9%)
YES, 0-5 Years	14 (14.4%)
YES, 6-10 Years	9 (9.3%)
YES, >10 Years	12 (12.4%)
YES, Duration Unknown	2 (2.1%)
Unknown	0
Donor Meets Expanded Criteria	26 (26.8%)

Table 2a.

Distribution of organs transplanted *

Organ	Transplanted
Kidney	78 (80.4%)
Lung	28 (28.9%)
Pancreas	22 (22.7%)
Liver	72 (74.2%)
Heart	37 (38.1%)

* Numbers in the table were counted in terms of donors (n=97), not organs.

Table 2b.

Number of organs transplanted from each donor

Number of organs	Number of donors	Cumulative
0	11	11 (11.3%)
1	7	18 (18.6%)
2	14	32 (33.0%)
3	18	50 (51.5%)
4	18	68 (70.1%)
5	13	81 (83.5%)
6	7	88 (90.7%)
7	6	94 (96.9%)
8	3	97 (100%)

A maximum of 8 organs (2 kidneys, 2 lungs, heart, liver, pancreas and intestine) were considered. In total 47 of 97 (48.5%) donors donated more than 3 organs which were transplanted.

Table 3.

Clinical variables selected in predictive models of transplantation of total number of organs and each organ

Outcome	Clinical Variable Set
Total number	Age+ History of Hypertension
Kidney	Age+ History of Hypertension+ History of Diabetes
Lung	Age+ Blood Type + History of Diabetes + Expanded Criteria [#]
Pancreas	Age+ History of Hypertension
Liver	Age+ Expanded Criteria [#] + Total Bilirubin+ ALT+ AST
Heart	Age+ History of Hypertension

Clinical variables were selected from full list(age, race, blood type, gender, history of diabetes, history of hypertension and expanded criteria for all organs; additional total bilirubin, AST, ALT and INR for liver) with cutoff P -value =0.2 and applied stepwise selection for multivariable models. ALT: aspartate aminotransferase. AST: alanine aminotransferase.

[#]: declared brain dead by use of hospital criteria for neurological determination of death, and age >60 y, or age between 50y and 59y, but with at least two of following complications (hypertension, death from cerebral vascular accident, sCr greater than 1.5mg/dl).

Table 4.Bootstrap *C*-statistics of models predicting transplantation of each organ *

	4A. Covariates for each model with <i>biomarkers</i> measured at enrollment (n=97)						
Outcome	IL-6 only	SLPI only	IL-6 +SLPI	Clinical variables ^a only	Clinical variables + IL-6	Clinical variables + SLPI	Clinical variables + IL-6 +SLPI
Total number	0.51 (0.39, 0.63)	0.52 (0.4, 0.62)	0.52 (0.41, 0.63)	0.86 (0.78, 0.92)	0.87 (0.79, 0.93)	0.86 (0.78, 0.92)	0.87 (0.79, 0.93)
Kidney	0.52 (0.37, 0.68)	0.61 (0.47, 0.76)	0.61 (0.45, 0.76)	0.86 (0.76, 0.95)	0.86 (0.76, 0.94)	0.86 (0.76, 0.94)	0.86 (0.76, 0.94)
Lung	0.52 (0.39, 0.64)	0.50 (0.39, 0.60)	0.52 (0.38, 0.64)	0.76 (0.67, 0.85)	0.77 (0.67, 0.85)	0.76 (0.67, 0.85)	0.77 (0.67, 0.85)
Pancreas	0.51 (0.36, 0.67)	0.52 (0.35, 0.67)	0.53 (0.36, 0.69)	0.89 (0.82, 0.96)	0.91 (0.84, 0.97)	0.89 (0.81, 0.96)	0.91 (0.84, 0.97)
Liver	0.52 (0.40, 0.67)	0.65 (0.52, 0.76)	0.66 (0.54, 0.76)	0.80 (0.69, 0.89)	0.80 (0.69, 0.9)	0.84 (0.74, 0.91)	0.84 (0.75, 0.92)
Heart	0.5 (0.38, 0.63)	0.52 (0.41, 0.63)	0.51 (0.38, 0.64)	0.80 (0.70, 0.88)	0.81 (0.72, 0.89)	0.80 (0.71, 0.88)	0.82 (0.73, 0.89)
	4B. Covariates for each model with <i>biomarkers</i> measured before ex-plantation (n=97)						
Outcome	IL-6 only	SLPI only	IL-6 +SLPI	Clinical variable only	Clinical variables + IL-6	Clinical variables + SLPI	Clinical variables + IL-6 + SLPI
Total number	0.48 (0.35, 0.60)	0.51 (0.39, 0.63)	0.53 (0.41, 0.64)	0.86 (0.78, 0.92)	0.86 (0.78, 0.92)	0.87 (0.80, 0.93)	0.87 (0.8, 0.94)
Kidney	0.51 (0.33, 0.70)	0.60 (0.43, 0.74)	0.60 (0.44, 0.74)	0.86 (0.76, 0.95)	0.85 (0.75, 0.95)	0.88 (0.77, 0.96)	0.88 (0.77, 0.96)
Lung	0.6 (0.47, 0.70)	0.54 (0.40, 0.66)	0.58 (0.45, 0.70)	0.76 (0.67, 0.85)	0.77 (0.67, 0.86)	0.78 (0.69, 0.87)	0.79 (0.70, 0.88)
Pancreas	0.48 (0.34, 0.61)	0.55 (0.41, 0.69)	0.54 (0.40, 0.68)	0.89 (0.82, 0.96)	0.90 (0.84, 0.96)	0.92 (0.86, 0.97)	0.92 (0.86, 0.97)
Liver	0.52 (0.38, 0.67)	0.65 (0.53, 0.78)	0.67 (0.55, 0.79)	0.80 (0.69, 0.89)	0.81 (0.70, 0.90)	0.85 (0.76, 0.92) [#]	0.86 (0.76, 0.93)
Heart	0.50 (0.38, 0.62)	0.55 (0.44, 0.67)	0.53 (0.40, 0.65)	0.80 (0.70, 0.88)	0.80 (0.71, 0.88)	0.80 (0.70, 0.88)	0.80 (0.70, 0.88)

Data were presented as Bootstrap *C*-statistic (95% CI).^a: clinical variables for each organ are shown in table 3.^{*}: Biomarkers are in log scale.[#]: adjusted OR (95% CI) for liver transplantation was 0.13 (0.03, 0.70), *P*=0.02

Table 5.Bootstrap *C*-statistics for Cox models predicting 3-years recipient survival^{*}

Time point	<i>C</i> -Statistics for each Cox model						
	IL-6 only	SLPI only	IL-6 +SLPI	Clinical variables ^a only	Clinical variables + IL-6	Clinical variables + SLPI	Clinical variables + IL-6 +SLPI
At enrollment	0.51 (0.38, 0.63)	0.50 (0.39, 0.60)	0.48 (0.34, 0.62)	0.59 (0.49, 0.69)	0.58 (0.45, 0.72)	0.58 (0.43, 0.72)	0.56 (0.40, 0.72)
Before ex-plantation	0.56 (0.44, 0.68)	0.51 (0.40, 0.63)	0.57 (0.45, 0.69)	0.59 (0.49, 0.69)	0.64 (0.50, 0.79) [#]	0.61 (0.45, 0.78)	0.64 (0.48, 0.80)

Data were presented as *C*-statistic (95% CI).^a: expanded criteria is the only clinical variable in modeling 3-years recipient survival, and *P*=0.007.[#]: adjusted HR (95% CI) for IL-6 was 1.26 (1.08, 1.48), *P*=0.004. For recipients, n=266. Event (death) =36.^{*}: Biomarkers are in log scale.