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

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on behalf of the Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) Study Investigators [1]

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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.
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 = .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.
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1. 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

Abbreviations: IL-6, interleukin-6; SLPI, secretory leukocyte protease inhibitor; IDI, integrated discrimination improvement; DND, donation after neurologic death; MOnIToR, 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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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.

2. 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 <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) (Fig. 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.

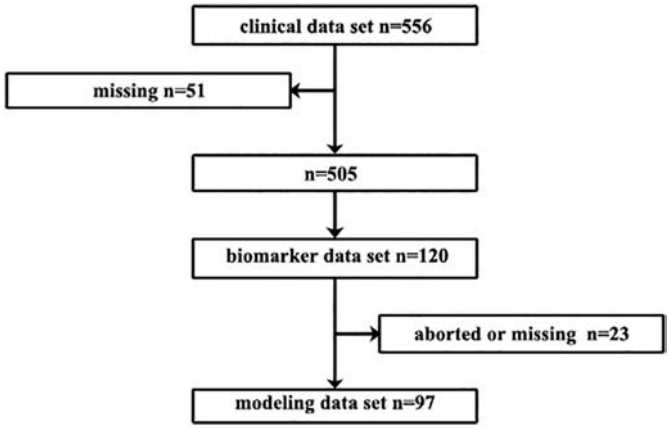

Fig. 1. Study flow and cohort selection. Out of 556 neurologically deceased organ donors, 505 donors had complete clinical data. From four clinical data sites, we collected plasma analysis (n = 120). After excluding missing or aborted data (n = 23), 97 donors containing both complete clinical and biomarker information were included in our final data set.

2.1. 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.

2.2. 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/).

3. 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