The impact of change in definition of increased-risk donors on survival after lung transplant

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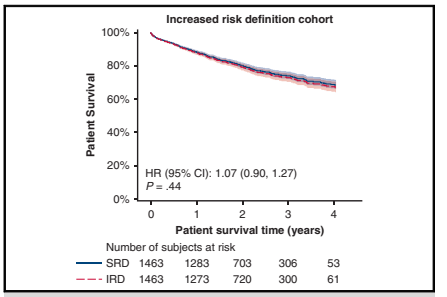
ABSTRACT

Objectives: To study the impact of using the US Public Health Service broadened definition of "increased-risk" donors (2013) in comparison with "high-risk" (1994) and standard infectious risk donors on lung transplant recipient outcomes.

Methods: Patients who underwent lung transplant between January 1, 2006, and May 31, 2017, in the Scientific Registry of Transplant Recipients were divided into 2 cohorts, recipients of: (1) high-risk donors: January 1, 2006, to October 1, 2013, and (2) increased-risk donors: January 1, 2014, to May 31, 2017, and compared with matched recipients who received standard-risk donors. Risks for acute rejection, patient, and graft survival using propensity score matched cohorts, multivariable logistic, and Cox models were examined.

Results: In total, 18,490 lung transplant recipients were analyzed with 36% transplanted during the increased-risk donor definition period. The proportion of donors classified as nonstandard infectious risk increased with the definition change (8% high-risk donors vs 22% increased-risk donors; $P < .001$). In both cohorts, male patients with a lower forced expiratory volume in 1 second and greater creatinine were more likely to receive an organ from increased risk donors. Neither graft nor patient survival differed by donor type in either period. Acute treated rejection within 1 year did not differ by period for recipients of increased risk donors (odds ratio, 0.87; $P = .23$) or recipients of high-risk donors (odds ratio, 1.2; $P = .27$).

Conclusions: The 2013 broadened definition of donor risk increased the proportion of nonstandard infectious risk donors. Recipients of increased/high-risk donors had similar graft and patient survival compared with standard-risk donors. (J Thorac Cardiovasc Surg 2020;160:572-81)



Patient survival by donor risk category. Survival was similar for recipients of standard-risk (*SRD*) and increased-risk donor (*IRD*) organs.

CENTRAL MESSAGE

The donor risk definition update in 2013 increased the number of donors classified as nonstandard risk. The use of increased-risk donors expands the donor pool without impacting survival.

PERSPECTIVE

Use of increased risk donors did not adversely impact posttransplant recipient outcomes. This questions the utility of the continued designation of "increased-risk donors," which is known to impact organ acceptance rates. Treating all donors as potentially at risk with diligent posttransplant screening protocols may increase organ use and decrease waitlist mortality.

See Commentaries on pages 582 and 583.

In 1994, the US Public Health Service (PHS) issued guidelines that identified "high-risk" donors (HRD) in an effort to reduce transmission of human immunodeficiency

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Abbreviations and Acronyms

CI = confidence interval
FEV1 = forced expiratory volume in 1 second
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus
HR = hazard ratio
HRD = high-risk donor
IRD = increased-risk donor
LAS = Lung Allocation Score
NAT = nucleic acid testing
OR = odds ratio
PHS = Public Health Service
SRD = standard-risk donor
SRTR = Scientific Registry of Transplant Recipients

virus (HIV) through organ transplant.[1] Prompting these guidelines was a 1991 investigation that revealed several HIV infections in organ-transplant recipients who had received a transplant from an HIV-seronegative donor.[2] In 2013, PHS updated its guidelines to identify donors not only at risk for HIV but also for hepatitis C virus (HCV) and hepatitis B virus (HBV).[3] The term HRD was replaced with "increased-risk donor" (IRD) in the 2013 guidelines to focus attention on the risk of incident (new cases of disease) rather than only prevalent disease because incident disease in the "window period" poses a greater risk of disease transmission.[4] This designation does not include donors who have a known infection with HIV, HCV, or HBV.

HRDs or IRDs have been used to expand the donor pool in lung transplantation, as shortage of organs accounts for approximately 10% of US lung transplant candidates dying on the waiting list each year.[5] However, stigma regarding acceptance of organs from HRD/IRD exists among patients and physicians. Refusal of IRD is a common occurrence, with 78.4% of waitlist candidates refusing an IRD organ offer, and is associated with a decreased rate of lung transplant.[6] The impact of broadening the definition from HRD to IRD in the United States on recipient outcomes has not been studied. This study aimed to test 2 hypotheses: (1) characteristics of HRD and IRD differ, and (2) use of HRD or IRD does not adversely impact patient survival (primary endpoint), graft survival, or incidence of acute rejection.

METHODS

Data Source

This study used data provided by the Scientific Registry of Transplant Recipients (SRTR) through a data use agreement. The SRTR receives data collected by the Organ Procurement and Transplantation Network under a contract from Health Resources and Services Administration. The SRTR collects data on every US organ donor, waitlist candidate, and transplant recipient. Information is gathered from organ-procurement organizations, transplant organizations, and histocompatibility laboratories with database supplementation from the National Technical Information Service's Death Master File and Centers for Medicare and Medicaid Services.[7]

Participants and Study Eligibility Criteria

Recipients undergoing lung transplant between January 1, 2006, and May 31, 2017, were identified from the SRTR database. Exclusion criteria included recipients who underwent lobar lung transplant, previous lung transplant recipients, <18 years of age at transplant, non-US citizens/residents who traveled to United States solely to receive transplant, had missing information on donor risk category, or were transplanted between October 1, 2013, and January 31, 2014 (the time period where either definition for nonstandard risk donors could be used) (Figure 1). Recipients were then divided into 2 cohorts based on which donor risk definition was used; transplant recipients from January 1, 2006, to October 1, 2013, were included in the HRD cohort, and transplant recipients from February 1, 2014, to May 31, 2017, were included in the IRD cohort. Variables were collected for recipients of HRD, IRD, and standard risk donors (SRD) for comparison.

Statistical Analysis

Continuous variables were evaluated for normality using the Shapiro–Wilk test. Normally distributed continuous measures were summarized using means and standard deviations and were compared between donor risk groups using analysis of variance. Non-normal continuous and ordinal measures were summarized using medians, 25th and 75th percentiles, and were compared between donor risk groups using the Kruskal–Wallis test. Categorical factors were compared using the Pearson χ^2 test. Group comparisons were analyzed using the original (non-matched) cohort. Missing values were imputed using fully conditional specification imputation methods. In each imputed data set (n = 10), propensity score matching was used to match HRD/IRD recipients to SRD (1:1 match).

Propensity Score

A logistic regression model was used to estimate the propensity score; having an HRD/IRD was modeled as the outcome with all recipient and donor characteristics as independent variables. Recipient characteristics included in the propensity score model were age, sex, body mass index, race, primary source of payment for transplant, median income in past 12 months by ZIP code, education, history of cigarette use, diabetes, Lung Allocation Score (LAS), lung disease group, Karnofsky functional group, life support, previous lung surgery, previous transplants for other organs, most recent serum creatinine, total bilirubin before transplant, forced expiratory volume in 1 second (FEV1) %, infection requiring intravenous drug therapy within 2 weeks before transplant, transplant year/definition of high risk, time on waiting list, total ischemic time, and procedure type. In addition, the following donor characteristics were also included: age, sex, body mass index, race, ABO group, alcohol use, history or recent use of cigarettes, cocaine, other drugs, death by stroke, death by non-beating heart. A greedy matching algorithm was used to select the best match from the same definition cohort for each recipient; all HRD/IRD recipients were matched. The standardized differences in all covariates before and after matching were evaluated to assess matching success (Figure 2).

Outcomes

The primary outcome was posttransplant patient survival. Secondary outcomes included graft survival and acute rejection (treated) within 1 year of transplant. Outcomes were assessed using the matched cohort. Patient and graft survival were evaluated using Cox regression with a robust sandwich covariance matrix estimate to account for intracluster

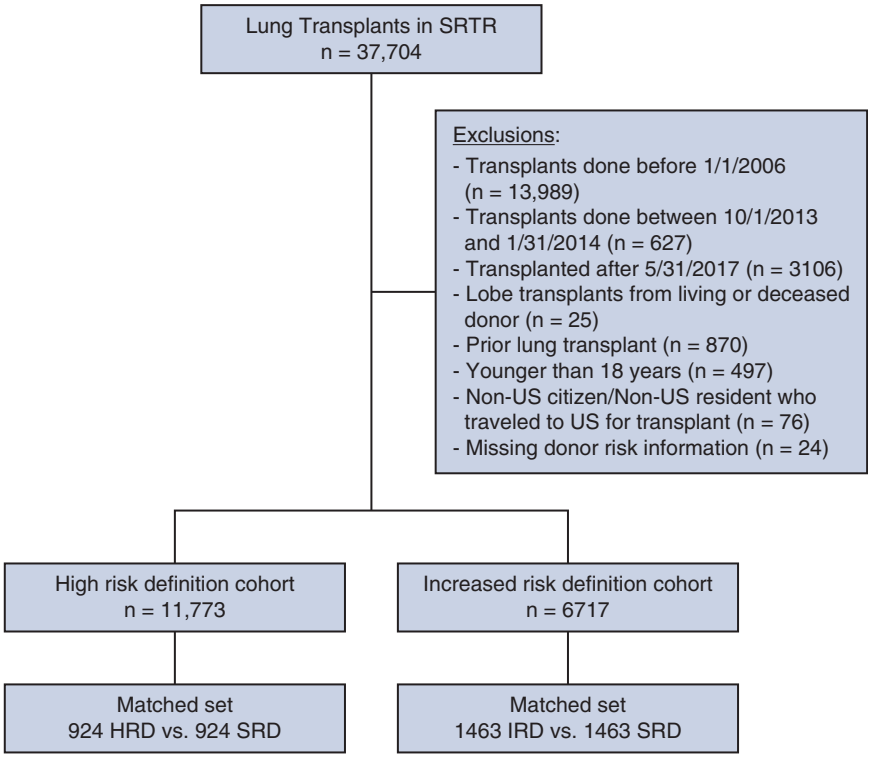

FIGURE 1. Flow diagram of the study population All lung transplant recipients between January 1, 2006, and May 31, 2017, were selected for analysis and divided into the high-risk donor cohort (January 1, 2006, to October 1, 2013) and increased-risk donor cohort (February 1, 2014, to May 31, 2017). The time frame when either classification could be used (October 1, 2013, to January 31, 2014) was excluded from analysis. *SRTR*, Scientific Registry of Transplant Recipients; *US*, United States; *HRD*, high-risk donor; *SRD*, standard-risk donor; *IRD*, increased-risk donor.

dependence due to matching. Posttransplant follow-up for the HRD cohort was truncated at 52 months, which was the maximum follow-up time in the IRD cohort. Acute rejection within 1 year of transplant was assessed using conditional logistic regression and was only assessed for subjects with 1 year of follow-up. All tests were 2-tailed and performed at a significance level of 0.05. Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Difference in Characteristics of IRD and HRDs (Original Cohort)

Donors in the HRD and IRD cohort differed from SRD by sex, race, history of heavy alcohol use, tattoos, history of cocaine use, cigarette use, and other drug use. IRDs were on average 1.5 years older than HRD and were more often female. There was a greater proportion of tattoos, other drug use, and hepatitis C antibody positivity in the IRD cohort compared to the HRD cohort. The IRD cohort had a lower proportion of donors with cigarette or cocaine use compared with donors in the HRD cohort (Table 1).

Comparison of HRDs and SRDs (Original cohort). Donor characteristics differed by risk designation with HRD, on average being 5 years younger in age, more commonly male, and white. The proportion of donor HCV antibody and donor HBV core antibody positivity did not differ between these groups (Table 1).

Comparison of IRDs and SRDs (Original cohort). Donor characteristics differed by risk designation, with IRDs on average being younger in age by average of 5 years, having a greater percentage of black donors, and more males compared with the SRD group. There was a greater proportion of donors that tested positive for hepatitis C antibody, but the proportion of donors positive for Hepatitis B core antibody did not differ between IRDs and SRDs (Table 1).

Difference in Characteristics of Recipients of Increased and HRDs (Original Cohort)

A total of 18,490 subjects were included in the analysis, with 64% transplanted during the HRD period (93 months) and 36% during the IRD period (40 months). Use of non-SRD increased during the IRD time period (22% vs 8%; $P < .001$) (Figure 3). Recipients of HRD and IRD differed compared with those who accepted SRD. Recipients of IRD were on average 2.5 years older than recipients of HRD. Compared with HRD recipients,

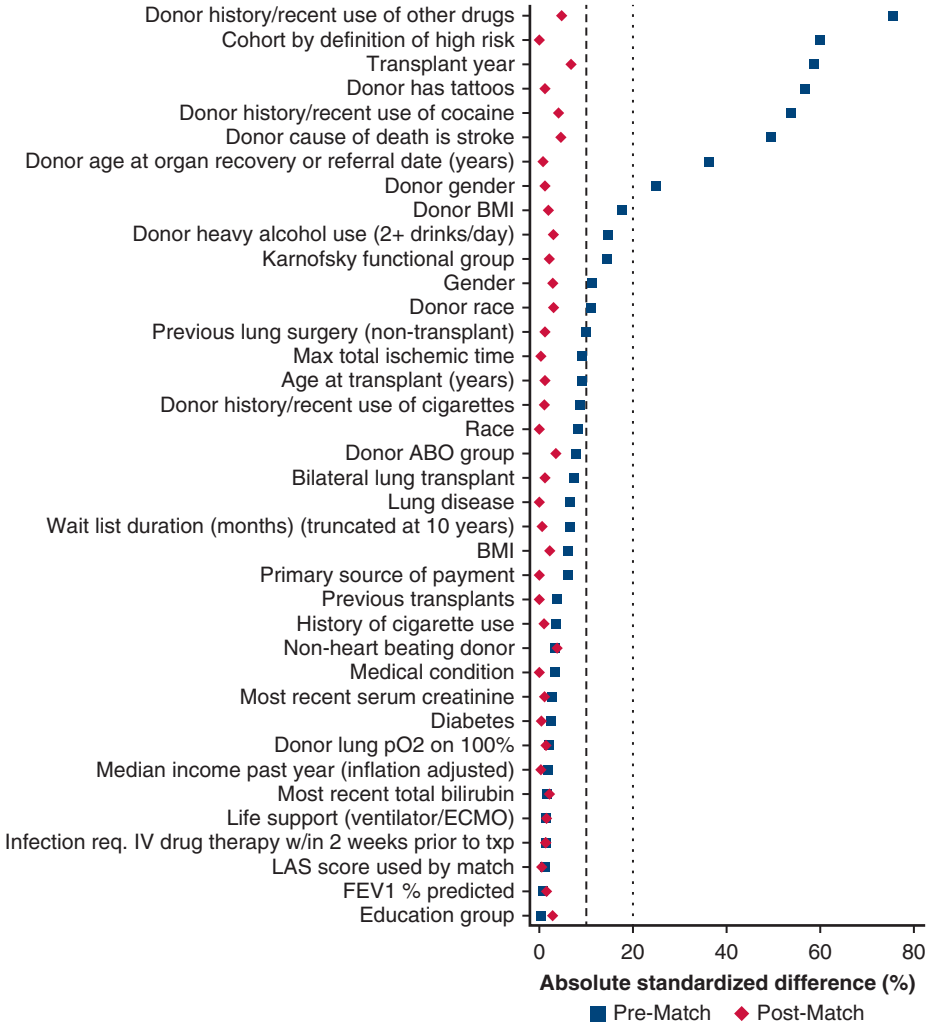

FIGURE 2. Standardized differences before and after matching. *Blue squares* indicate the prematch characteristics (original cohort, n = 18,490), and *red diamonds* indicate the postmatch comparison (matched cohort, n = 4774). The *dashed* and *dotted lines* represent absolute standardized differences of 10% and 20%. *BMI*, Body mass index; *max*, maximum; pO_2, partial pressure of oxygen; *ECMO*, extracorporeal membrane oxygenation; *IV*, intravenous; *LAS*, Lung Allocation Score; *FEV1*, forced expiratory volume in 1 second.

recipients of IRD included a greater proportion of female patients and individuals with a high school education or less. IRD recipients on average had a greater LAS and included more patients with group D diagnoses (restrictive lung diseases) and a slightly greater LAS compared with HRD recipients.

Comparison of recipients of HRDS and SRDs (Original cohort). Recipients of HRD comprised a greater percentage of men (64.9% vs 58.9%) and more commonly received bilateral lung transplant (71.5% vs 66.4%) compared with SRD recipients. Type of lung disease differed between HRD and SRD recipients, with a greater proportion of those with group A diagnoses (chronic obstructive pulmonary disease) and a lower proportion of group D disease in the HRD cohort. There was not a significant difference in age, LAS, waitlist duration, use of life support, or race between HRD and SRD recipients. Education level, insurance type, and median income did not differ by group. HRD recipients had a lower FEV1 and a slightly greater creatinine compared with SRD recipients (Table 2).

Comparison of recipients of IRDs and SRDs (Original cohort). Recipients of IRD organs were older on average and an increased proportion of recipients were men compared with SRD recipients. IRD recipients were more likely to be former cigarette smokers and achieved a lower level of education. Race, median income, and insurance type did not differ between IRD and SRD groups. Primary lung disease differed by group with a greater proportion of group A (chronic obstructive pulmonary disease) and lower proportion of group C (cystic fibrosis) receiving IRD organs. Recipient LAS,

TABLE 1. Donor characteristics for HRD (1994 guidelines) and IRD (2013 guidelines)

Donor characteristics	HRD cohort SRD (n = 10,849)	HRD cohort HRD (n = 924)	HRD cohort *P* value	IRD cohort SRD (n = 5254)	IRD cohort IRD (n = 1463)	IRD cohort *P* value	HRD vs IRD *P* value
Donor age, y	34.7 ± 14.4	29.6 ± 10.8	**<.001***	36.1 ± 14.6	31.1 ± 10.7	**<.001***	**.001***
Male sex	6402 (59.0)	670 (72.5)	**<.001**†	3074 (58.5)	1016 (69.4)	**<.001**†	.11†
Race			**<.001**†			**<.001**†	.089†
White	6637 (61.2)	612 (66.2)		3206 (61.0)	905 (61.9)		
Black	2180 (20.1)	185 (20.0)		990 (18.8)	326 (22.3)		
Hispanic	1665 (15.3)	111 (12.0)		832 (15.8)	190 (13.0)		
Other	367 (3.4)	16 (1.7)		226 (4.3)	42 (2.9)		
Blood type			**.007**†			.30†	.16†
A	3910 (36.0)	302 (32.7)		1946 (37.0)	528 (36.1)		
AB	232 (2.1)	19 (2.1)		108 (2.1)	35 (2.4)		
B	1183 (10.9)	80 (8.7)		576 (11.0)	141 (9.6)		
O	5524 (50.9)	523 (56.6)		2624 (49.9)	759 (51.9)		
Donor BMI	25.8 ± 5.2	24.8 ± 4.3	**<.001***	26.5 ± 5.4	25.4 ± 4.7	**<.001***	**.002***
Heavy alcohol use (≥2 drinks/d)	1345 (12.5)	163 (18.2)	**<.001**†	752 (14.5)	259 (18.6)	**<.001**†	.81†
Tattoos	3485 (32.2)	513 (55.9)	**<.001**†	2161 (41.2)	972 (66.9)	**<.001**†	**<.001**†
History of cigarette use	1108 (10.3)	139 (15.5)	**<.001**†	358 (6.9)	136 (9.7)	**<.001**†	**<.001**†
Cocaine use	1039 (9.7)	292 (33.4)	**<.001**†	600 (11.5)	431 (31.0)	**<.001**†	.24†
Other drug use	3331 (30.9)	564 (63.4)	**<.001**†	1946 (37.1)	1035 (72.9)	**<.001**†	**<.001**†
Donation after cardiac death	135 (1.2)	10 (1.1)	.67†	172 (3.3)	47 (3.2)	.91†	**<.001**†
Stroke as cause of death	4120 (38.0)	168 (18.2)	**<.001**†	1878 (35.7)	215 (14.7)	**<.001**†	**.024**†
Hepatitis C antibody positive	4 (0.04)	1 (0.11)	.34†	4 (0.08)	10 (0.68)	**<.001**†	**.049**†
Hepatitis B core antibody positive	247 (2.4)	24 (2.7)	.63†	139 (2.6)	33 (2.3)	.41†	.49†
Ischemic time	297.0 [238.0, 362.0]	308.0 [247.0, 372.0]	**.002**‡	303.0 [240.0, 369.0]	306.0 [240.0, 376.0]	.25‡	.64‡

Statistics presented as mean ± standard deviation, median [25th and 75th percentiles], or n (column %). Bold indicates statistically significant values. *P* values: *analysis of variance; †Pearson χ^2 test; ‡Kruskal–Wallis test. *HRD*, High-risk donor, *IRD*, increased-risk donor; *SRD*, standard-risk donor; *BMI*, body mass index.

time on the waiting list, and use of life support did not differ for those accepting IRD compared with SRD. Recipient creatinine, FEV1, and transplant type did not differ between IRDs and SRDs (Table 2).

Patient and Graft Survival (Matched Cohort)

Patient survival was similar between HRD and SRD recipients (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.83-1.14, $P = .73$) as well as between IRD and SRD recipients (HR, 1.07; 95% CI, 0.90-1.27, $P = .44$). The change in definition had no statistically significant impact on the association between HRD/IRD and patient mortality (interaction term $P = .44$) (Figure 4). Graft survival was similar between HRD and SRD recipients (HR, 0.99, 95% CI, 0.85-1.16, $P = .93$) as well as between IRD and SRD recipients (HR, 1.07; 95% CI, 0.90-1.26, $P = .44$). Broadening the definition of nonstandard risk donors had no statistically significant impact on the association between HRD/IRD and graft survival (interaction term $P = .55$) (Figure 4).

Acute Treated Rejection (Matched Cohort)

There was no association between HRD/IRD and acute rejection within 1 year. Patients receiving an organ from an HRD had similar incidence of rejection compared with those who received an organ from an SRD (odds ratio [OR], 1.2; CI, 0.86-1.68, $P = .27$). There was also no association in the IRD cohort (OR, 0.87; CI, 0.69-1.10, $P = .23$). The relationship between donor risk and acute rejection did not change by period (interaction term $P = .054$) (Figure 5).

DISCUSSION

Principal Findings

In this study, we show that the use of lungs from donors defined as increased risk based on the broader 2013 IRD

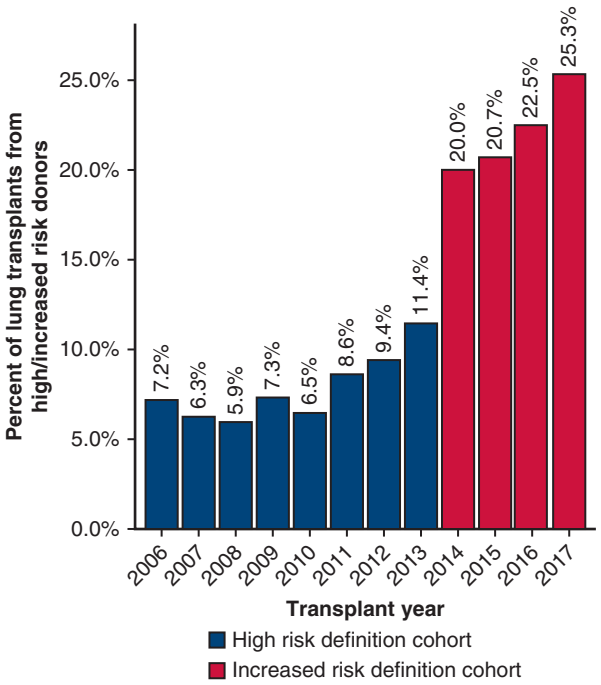

FIGURE 3. High/increased-risk donor organ use over time. The use of the high-risk definition (*blue*) occurred from 2006 to 2013 and the increased risk definition (*red*) occurred from 2014 to 2017 (original cohort, n = 18,490). Note: Not all transplants in 2013, 2014, and 2017 were included as described in the Methods.

definition compared with the 1994 HRD definition was not associated with decreased posttransplant patient or graft survival. Donor characteristics differed by cohort, which may be due to the implementation of a definition change that was more broad, sensitive to HCV and HBV risk, and focused on detecting incident in addition to prevalent disease. This study adds to the current literature by studying the impact of a new broader definition for donor risk in lung transplantation using propensity score methodology to account for potential baseline differences in recipients who accept an organ from an HRD/IRD.

Impact of Policy Change

Studying the impact of policy change, in this case, the broadening of definition of donor risky behavior that has the potential to change organ acceptance rates, is important to ensure that unintended system-wide effects are identified. High-risk or increased-risk designation is used to identify risky donor behavior with the goal to reduce the transmission of HIV, HBV, and HCV.[8] With the broadening of definition in 2013, there was a significant change in the proportion of transplanted organs from IRD compared to HRD in the previous cohort (22% vs 8%; $P < .001$). It has been previously shown that the rate of refusal for at least one HRD/IRD lung offer was not only common but associated with an increased time to transplant and waitlist mortality.[6] More transplants using lungs from IRD occurred during the 2013 definition period compared with HRD transplants in the 1994 definition period but organ offer acceptance rates were not available in this dataset. Therefore, it is not known if changes in organ offer acceptance rates contributed to a difference in the number of transplants performed.

Impact of Change in Defining Donor Risk on Posttransplant Outcomes

We compared survival at 1 year between SRD and HRD, SRD and IRD, and between eras. The finding of equivalent survival between SRD and HRD in the "high-risk" definition era is corroborated by a previous study evaluating patient survival from January 2005 to June 2013 but did not include the "increased-risk" era.[9] Our study additionally accounted for potential differences in recipients, such as severity of illness, diagnosis type, or age by using propensity score matching. There was no difference in 1-year patient or graft survival between eras. As in this study, the use of non-SRD organs did not adversely impact patient or graft survival in studies of heart, kidney, and liver transplant recipients.[10-12] In addition, receipt of a HRD/IRD compared with an SRD was not associated with an increased likelihood of acute rejection within 1 year.

Concern for transmission of HBV, HCV, and HIV limits the use of donor organs that are otherwise appropriate for transplant. Despite the label of "increased risk" or "high risk," studies evaluating the undetected risk of window period infections have shown these risks to be quite low. In a study of window period HIV infection from HRDs, pooled incidence estimates were 0.09 to 12.1 per 10,000 based on enzyme-linked immunosorbent assay and 0.04 to 4.9 per 10,000 donors based on nucleic acid testing (NAT).[13] Similarly, these risks have been identified for window period HCV with pooled incidence rates of 0.26 to 300.6 based on enzyme-linked immunosorbent assay and 0.027 to 32.4 with NAT, which reduces the window between infection and a positive test result when compared with antibody testing.[14,15] Use of NAT may be associated with increased willingness of physicians to accept IRD organs (OR, 1.58 for HIV and OR, 2.69 for HCV).[16] A study of kidney transplant candidates demonstrated that patients felt unprepared to consider a nonstandard infectious risk donor, and 79% of patients reported increased willingness to accept an organ from a HRD after being provided with more education and information.[17]

Limitations

Limitations of this study include the inequality of cohort sizes, with 64% transplanted during the HRD era whereas 36% were transplanted during the IRD era. Follow-up in the HRD cohort was truncated at 52 months, the maximum

TABLE 2. Recipient characteristics for HRD (1994 guidelines) and IRD (2013 guidelines)

Recipient characteristics	HRD cohort			IRD cohort			HRD vs IRD
	SRD (n = 10,849)	HRD (n = 924)	*P* value	SRD (n = 5254)	IRD (n = 1463)	*P* value	*P* value
Recipient age at transplant, y	54.9 ± 13.1	55.1 ± 13.4	.73*	56.6 ± 12.9	57.6 ± 12.0	**.007***	**<.001***
Male sex	6392 (58.9)	600 (64.9)	**<.001**†	3070 (58.4)	932 (63.7)	**<.001**†	.54†
Race			.63†			.21†	.32†
White	9088 (83.8)	788 (85.3)		4253 (80.9)	1209 (82.6)		
Black	946 (8.7)	75 (8.1)		486 (9.3)	134 (9.2)		
Hispanic	598 (5.5)	43 (4.7)		361 (6.9)	90 (6.2)		
Other	217 (2.0)	18 (1.9)		154 (2.9)	30 (2.1)		
Cigarette use	6624 (62.5)	579 (63.7)	.49†	3007 (57.3)	903 (61.7)	**.002**†	.33†
Education (high school or less)	4242 (43.1)	332 (39.8)	.063†	1996 (39.1)	622 (43.3)	**.004**†	.11†
Median income past 12 mo (inflation adjusted)	56,741.0 [45,031.0, 74,302.0]	53,967.0 [43,395.0, 73,323.0]	**.013**‡	57,786.0 [45,779.0, 75,394.0]	57,386.0 [44,590.0, 76,344.0]	.33‡	**.019**‡
Insurance			.58†			.75†	**.016**†
Private	4841 (44.6)	428 (46.3)		2745 (52.2)	766 (52.4)		
Public	5938 (54.7)	491 (53.1)		2491 (47.4)	690 (47.2)		
Other	70 (0.65)	5 (0.54)		18 (0.34)	7 (0.48)		
Lung disease			.050†			**.026**†	**<.001**†
A	3506 (32.3)	334 (36.1)		1413 (26.9)	421 (28.8)		
B	486 (4.5)	31 (3.4)		175 (3.3)	51 (3.5)		
C	1369 (12.6)	119 (12.9)		617 (11.7)	132 (9.0)		
D	5488 (50.6)	440 (47.6)		3049 (58.0)	859 (58.7)		
Match LAS	39.9 [34.7,49.8]	39.3 [34.5, 51.5]	.66‡	41.4 [35.3,54.1]	40.7 [34.8,51.9]	**.019**‡	**.030**‡
IV antibiotic therapy ≤2 wk before transplant	1086 (10.4)	112 (12.5)	**.048**†	590 (11.3)	129 (8.9)	**.009**†	**.006**†
Creatinine	0.85 ± 0.38	0.87 ± 0.49	**.046***	0.85 ± 0.50	0.85 ± 0.31	.99*	.11*
FEV1	38.5 ± 20.9	36.9 ± 20.6	**.026***	39.6 ± 20.6	40.3 ± 21.3	.25*	**<.001***
Life support (ventilator/ ECMO)	744 (6.9)	65 (7.0)	.84†	400 (7.6)	113 (7.7)	.89†	.53†
Hospitalization			.87†			.19†	**.017**†
ICU	927 (8.5)	83 (9.0)		658 (12.5)	179 (12.2)		
Hospitalized (non-ICU)	866 (8.0)	71 (7.7)		557 (10.6)	132 (9.0)		
Outpatient	9056 (83.5)	770 (83.3)		4039 (76.9)	1152 (78.7)		
Waitlist duration, mo	2.2 [0.66,6.9]	2.0 [0.59,7.4]	.099‡	1.9 [0.56, 5.7]	1.7 [0.49, 5.3]	.060‡	**.026**‡
Bilateral lung transplant	7203 (66.4)	661 (71.5)	**.001**†	3782 (72.0)	1047 (71.6)	.75†	.99†

Statistics presented as mean ± standard deviation, median [25th and 75th percentiles]. Bold indicates statistically significant values. *P* values: *analysis of variance; †Pearson χ^2 test; ‡Kruskal–Wallis test. *HRD*, High-risk donor, *IRD*, increased-risk donor; *SRD*, standard-risk donor; *LAS*, Lung Allocation Score; *IV*, intravenous; *FEV1*, forced expiratory volume in 1 second; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit. or n (column %).

follow-up in the IRD cohort, and this study is limited in assessing patient or graft survival beyond this follow-up interval. All lung transplants in this analysis were screened for acceptance, which represents a selection bias by the accepting center. We are aware that there are center-level differences in this practice, but this analysis focused on national acceptance practices and its impact on outcomes. It has been shown that risk level within non-SRDs differs by behavior type (injection drug use, high risk sexual behavior, men who have sex with men, incarceration, etc), which impacts the risk of transmission of HCV and HIV. The Organ Procurement and Transplantation Network does not collect all donor risk behavior limiting variables available in the SRTR dataset; therefore, these subdivisions of risk level were not accounted for in this study limiting our ability to determine if risk level differed by these uncaptured donor behaviors.[13,14] In addition, acute treated rejection in the first year was chosen as an endpoint without further granularity because that is how rejection is captured in the SRTR database. This analysis does not consider the

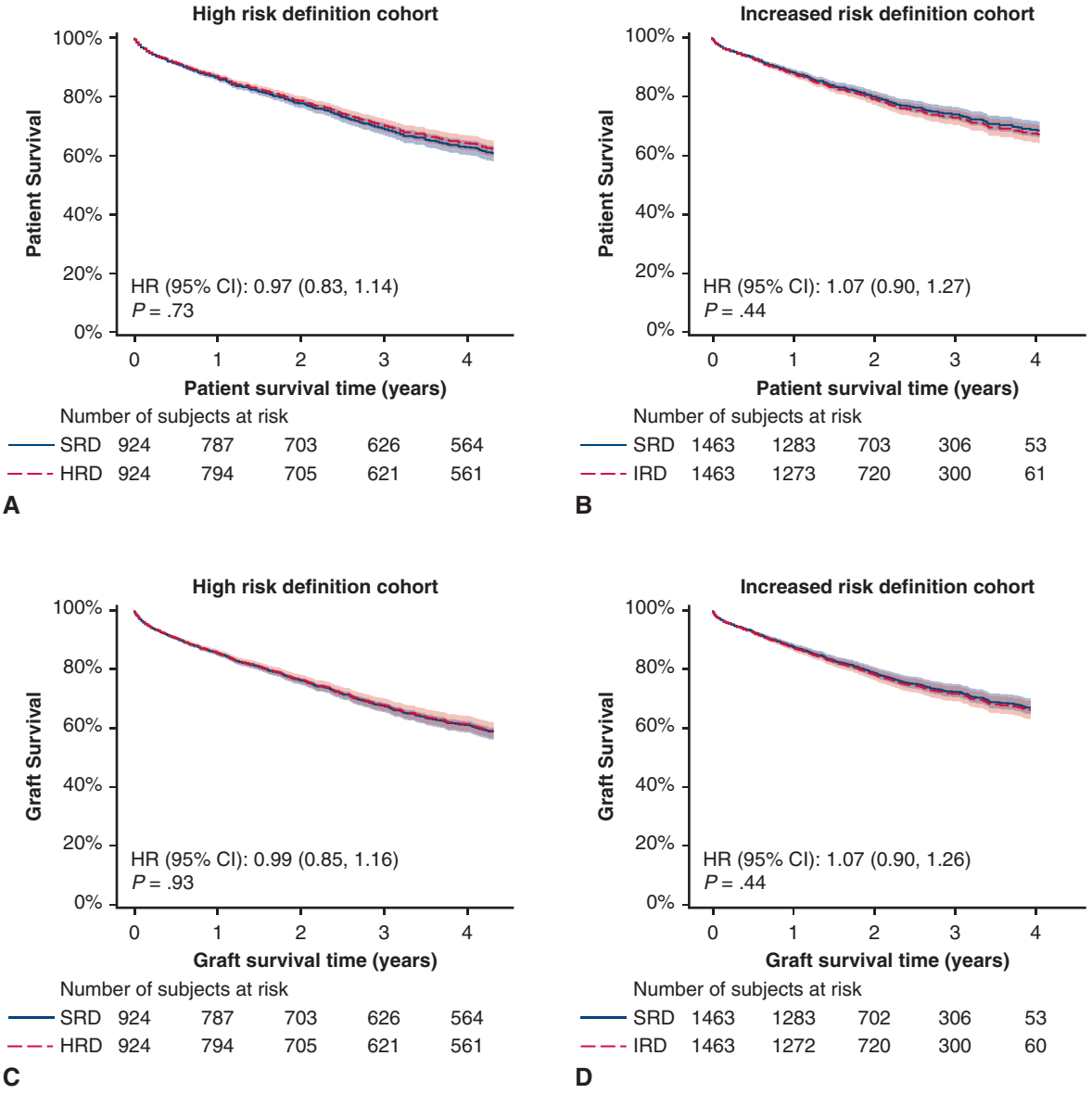

FIGURE 4. Patient and graft survival by donor risk category. A, Patient survival by donor risk in the HRD cohort (matched cohort, n = 1848). B, Patient survival by donor risk in the IRD cohort (matched cohort, n = 2926). C, Graft survival by donor risk in the HRD cohort (matched cohort, n = 1848). D, Graft survival by donor risk in the IRD cohort (matched cohort, n = 2926). Patient and graft survival did not differ between HRD/IRD and SRD in either cohort. *HRD*, High-risk donor; *SRD*, standard-risk donor; *IRD*, increased-risk donor.

heterogeneity between the levels of rejection prompting treatment by an individual center and the specific treatment regimen.

Finally, this study is an analysis of the impact of use of high/increased risk donors on US lung transplant recipient population. It is important to note that there is a 10-fold greater rate of drug-related deaths in the United States compared with Europe and 2-fold greater rate compared with Canada, which may limit the generalizability of these findings; however, donor risk is dichotomized in both Europe and Australia as it is done in the United States.[18,19] Although centralized posttransplant surveillance is less robust internationally, it has been identified as a guiding principle by the World Health Organization's Guiding Principles on Transplantation and the concepts discussed in our findings may have international applicability.[19]

CONCLUSIONS

The number of nonstandard risk donors increased with the definition change from the 1994 PHS "high-risk" to

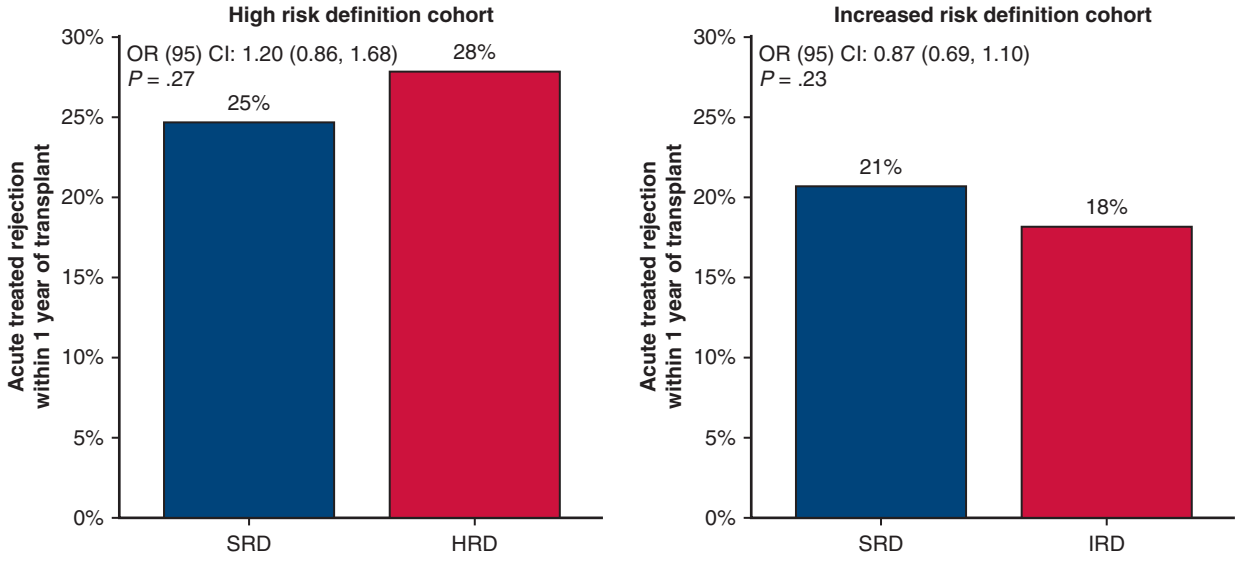

FIGURE 5. Acute treated rejection within 1 year of transplant. The percentage of patients who experienced a treated episode of acute rejection in 1 year after transplant between A, SRD and HRD (matched cohort, n = 1848) and B, SRD and IRD (matched cohort, n = 2926). There was not a significant association between HRD/IRD and acute rejection within 1 year of transplant, and the interaction term between donor risk group and period cohort was not statistically significant (interaction term $P = .054$). *SRD*, Standard-risk donor; *HRD*, high-risk donor; *IRD*, increased-risk donor.

the 2013 "increased-risk" donors, and combined with the known high percentage of refusal of HRD/IRD offers, there is the potential to further narrow the available donor pool for lung transplant candidates. We show that even with broadening the definition of donor risk, neither graft nor patient survival was compromised (Figure 6 and Video 1).

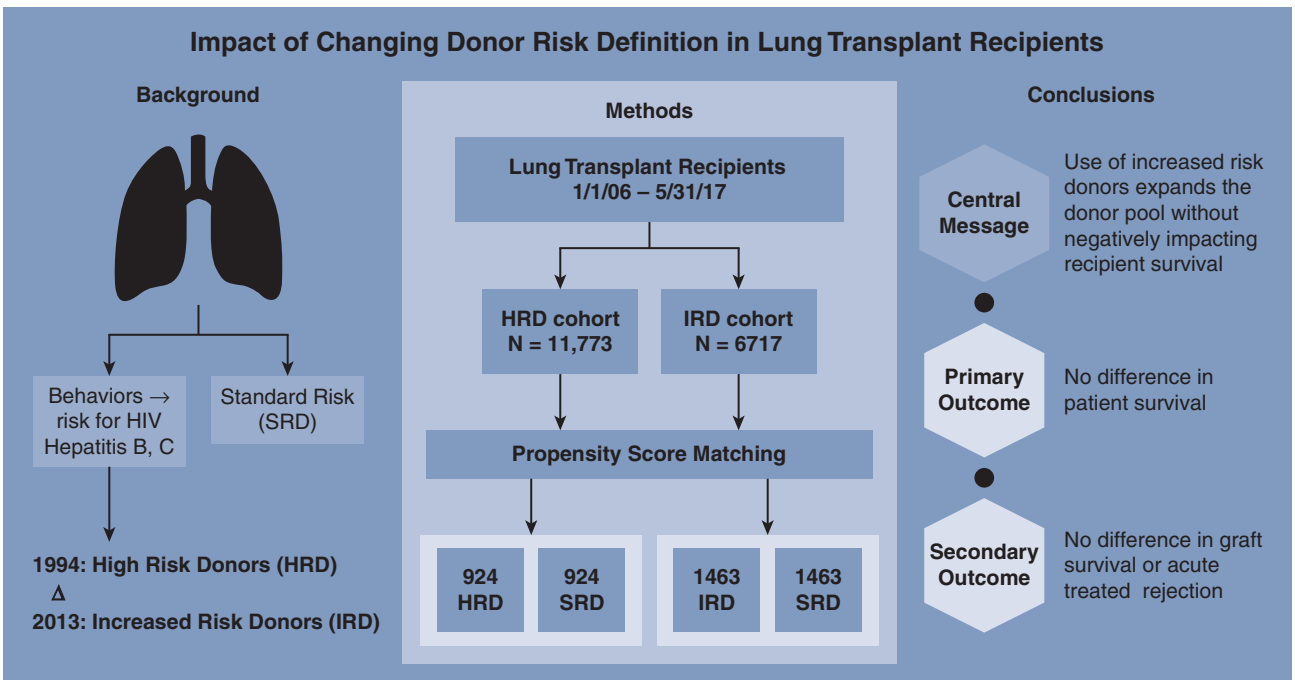

FIGURE 6. Background, study methods, and study conclusions. Donors at elevated risk for human immunodeficiency virus (*HIV*), hepatitis B virus (HBV), and hepatitis C virus (HCV) defined by Public Health Service (PHS) as high-risk donor (*HRD*) in 1994, which was changed to a more inclusive definition of increased-risk donor (*IRD*) in 2013 (*left panel*). Cohort selection and propensity matching are summarized in the *middle panel*. The *right panel* highlights the central message, primary, and secondary outcomes. *SRD*, Standard-risk donor.

VIDEO 1. Video abstract discussing methods, results, key findings, and conclusions. Video available at: https://www.jtcvs.org/article/S0022-5223(19)33064-8/fulltext.

These findings raise the question of the utility of the designation of "increased-risk" criteria for donor lungs. Currently, transplant candidates must provide consent for receiving these nonstandard risk donors, which leads to decreased organ use and increased waitlist mortality, despite evidence that posttransplant patient/graft survival and risk of rejection are equivalent to SRDs. The risk of undetected infection with NAT testing is less than 1 in 1 million for HIV after 14 days, HBV after 35 days, and HCV after 7 days from the time of most recent exposure to the time of negative NAT.[20] The risk of disease transmission to organ transplant recipients is quite low, with widespread use of NAT testing in donors with 7 documented HBV, 20 HCV, and no cases of HIV transmissions across all organ transplants performed in the United States from 2014 to 2017.[21] Foregoing the "increased risk" designation and treating all donors as potentially at risk with appropriate posttransplant screening for HBV, HCV, and HIV may increase organ use rates and decrease waitlist mortality.

Conflict of Interest Statement

All authors have nothing to disclose with regard to commercial support.

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Key Words: organ donation, increased risk donors, transplant outcomes