ORIGINAL ARTICLE

Between-center disparities in access to heart transplantation in France: contribution of candidate and center factors — A comprehensive cohort study

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SUMMARY

Transplantation represents the last option for patients with advanced heart failure. We assessed between-center disparities in access to heart transplantation in France 1 year after registration and evaluated the contribution of factors to these disparities. Adults (n = 2347) registered on the French national waiting list between January 1, 2010, and December 31, 2014, in the 23 transplant centers were included. Associations between candidate and transplant center characteristics and access to transplantation were assessed by proportional hazards frailty models. Candidate blood groups O and A, sensitization, and body mass index ≥30 kg/m^2 were independently associated with lower access to transplantation, while female gender, severity of heart failure, and high serum bilirubin levels were independently associated with greater access to transplantation. Center factors significantly associated with access to transplantation were heart donation rate in the donation service area, proportion of high-urgency candidates among listed patients, and donor heart offer decline rate. Between-center variability in access to transplantation increased by 5% after adjustment for candidate factors and decreased by 57% after adjustment for center factors. After adjustment for candidate and center factors, five centers were still outside of normal variability. These findings will be taken into account in the future French heart allocation system.

Transplant International 2018; 31: 386–397

Key words
access to transplantation, heart allocation system, heart transplantation, proportional hazards frailty models

Received: 9 August 2017; Revision requested: 20 September 2017; Accepted: 8 November 2017; Published Online 1 December 2017

Introduction

Heart transplantation is considered to be a life-saving procedure for carefully selected patients with advanced heart failure refractory to other treatments [1–3]. However, the limited number of donors together with the increasing donor heart demand result has resulted in restricted access to transplantation in the majority of countries [4]. In the United States, the new heart allocation system expands the number of allocation statuses, accounts for severity of illness, focuses on patient physiology and the emerging population of ventricular assist device (VAD) patients, and considers geographic variations in heart allocation [5], whereas in Eurotransplant, patients with high urgency are prioritized by waiting time and medical urgency [6,7].

doi:10.1111/tri.13093

Since 2004, the allocation system in France is based on urgency, offering donor organs to candidates at the highest risk of waitlist mortality, and donation service areas (DSAs). When a donor heart has not been allocated to an urgent patient, it is first offered to a local center, and, if it is declined locally, it is then offered to centers located in the regional DSA, and finally nationwide to centers in other regions (Fig. 1). In 2015, only 471 heart transplantations were performed for 980 candidates (49%). Fifty-six percent of candidates who underwent heart transplantation in France presented high-urgency (HU) status at the time of transplantation, indicating a breaking point of the system. At the same time, a recent study has identified patient categories not well covered by the current allocation system and less likely to receive a transplant, such as blood group O or high body mass index (BMI) candidates [8].

The French allocation rules are currently under review to develop a more effective and more equitable allocation system.

Geographic disparities in access to organ transplantation based on waiting time and deaths on waiting lists have been recognized for a long time in France [9–11] and in other countries [12–19]. Nevertheless, few studies have investigated both individual and center factors more specifically affecting access to heart transplantation [9,11,15].

One hypothesis to explain these disparities could be related to differences in candidate characteristics, center registration rates and practices, center donor heart offer decline rates, and regional variability in organ donation rates. Proportional hazards frailty models were used to measure between-center variability and explain part of the candidate and center variability, taking into account the short transplantation waiting time during the year after registration.

This study was designed to assess the between-center variability in access to transplantation and identify candidate and center factors contributing to these disparities.

Materials and methods

Study population

All patients from metropolitan France over the age of 18 years and registered on the heart transplantation waiting list between January 1, 2010, and December 31, 2014, were included. Patients waiting for a combined transplantation (including heart and lung transplantation) were excluded.

Data source

Data were extracted from CRISTAL, the national database managed by the *Agence de la Biomédecine* (national transplant agency) that prospectively collects demographic and medical information about patients registered on the French waiting list. Candidate data must be entered by transplant teams and validated by the *Agence de la Biomédecine* using a high-quality system, as CRISTAL is primarily used for graft allocation. Withdrawal from the waiting list and candidate deaths must be prospectively notified. This study was conducted in accordance with French law.

Variables

Patient characteristics

All patient clinical characteristics collected at registration and associated with access to transplantation during the year after registration on the heart waiting list were considered [8].

Missing values for relevant covariates were replaced by values obtained by multiple imputations according to a Markov chain Monte Carlo approach with uninformative prior information (SAS MI procedure) [8]. An analysis keeping missing data as modality was performed and with same results but with wider confidence intervals.

Center characteristics

As grafts that are not allocated to an urgent patient are currently offered to local and regional centers, heart donation rates (reported to the French general population) and number of centers in the donation service area were used to depict center access to heart grafts. The proportion of candidates living in other donation service areas (seven regional DSA in France) among the patients listed in the center was used to reflect the center's drawing power. The center donor heart offer decline rate and the proportion of heart transplants procured from outside of the center's DSA were considered to be markers of the center's graft acceptance policy. The center donor heart offer decline rate was defined as the proportion of hearts declined among the hearts offered to a center, excluding nontransplanted grafts. Center registration practices were described by the number of candidates registered in the center and the proportion of high-urgency candidates among listed patients. Each continuous variable was divided into two

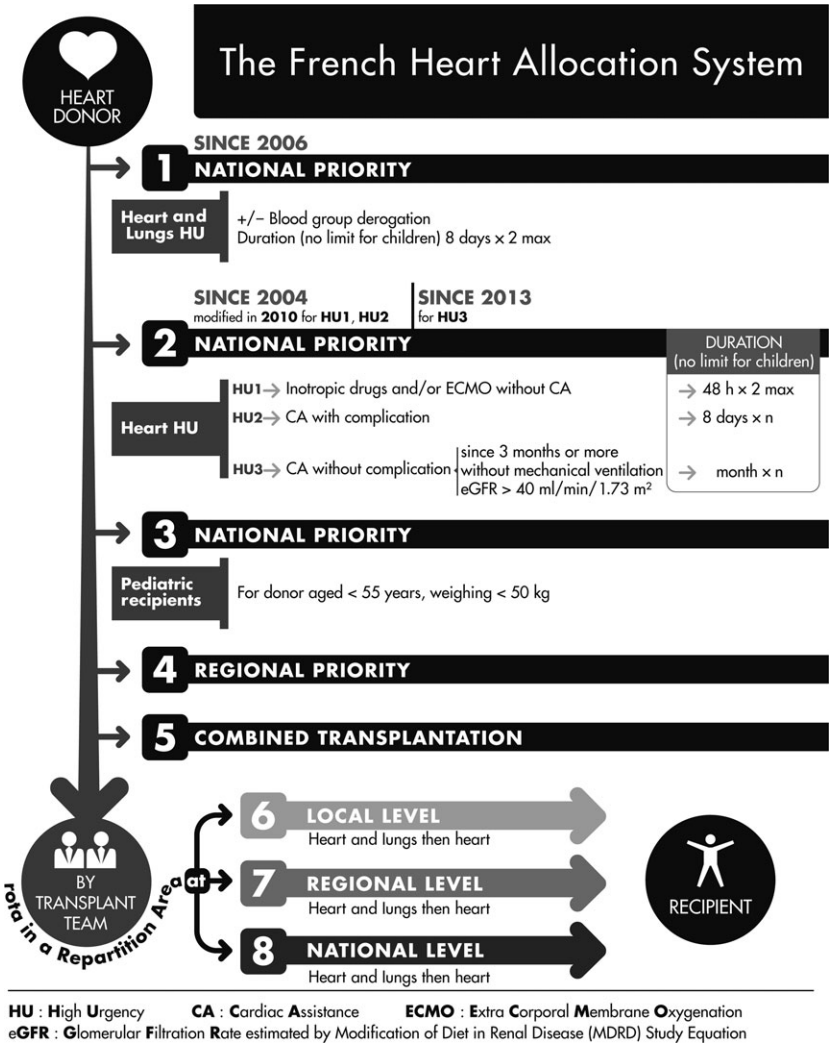

Figure 1 Schematic representation of the French heart allocation system. Preference is given to high-priority (HU) patients waiting for heart–lung transplant. Priority access is given to candidates on circulatory support (IV inotropic support, ECMO), and at high risk of requiring a ventricular assist device (VAD) or total artificial heart (HU1), or candidates who have had an infection or complication after VAD (HU2). Children then have priority access to transplantation based on their specific characteristics (morphology and morbidity): Organs from a donor under the age of 55 years old and weighing less than 50 kg are preferentially allocated to a child. In the absence of priorities and the need for a combined transplantation, the order of organ offers is based on a rotation that allows for local variations and practices within a hierarchy from local (same hospital or network) to regional or national levels.

categories: highest quartile vs. other quartiles. Thereby, the effects of all center variables were standardized by a comparison of the risks of transplantation from observations at the higher quartile and other quartiles for each center variable.

Statistical analysis

Patient characteristics by center as well as center characteristics of each center were represented graphically to depict variability across centers. Three separate shared frailty survival models including transplantation centers as random effect parameters (center effect with residues following normal distribution) were created in order to evaluate the between-center variability in access to transplantation during the year after registration on the waiting list and to assess the contribution of patient and center characteristics to this variability [20,21]. The estimate and the asymptotic standard error of the common variance parameter of the normal random effect in each model were estimated with the maximum likelihood method. The time period considered was the duration between registration on the heart waiting list and transplantation. Patients who died or who were delisted due to worsening medical condition were censored at the date of the event; event-free patients consisting of those who remained on the waiting list were censored 1 year after registration.

The first model included only transplantation centers as random effect parameters (Model 1). Candidates (Model 2) and center characteristics (Model 3) were then progressively added. The progressive variation in the estimated variability of the center effect was used to quantify the contribution of candidate and center characteristics to the between-center variability. Random effect estimates were represented graphically in order to compare access to transplantation between centers, after adjustment for patient and center characteristics. For

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each of three models, the individual prediction of the center effect on access to transplantation is expressed as a hazard ratio (HR): Centers with a HR > 1 (HR < 1) tended to access transplantation at a faster (lower) rate than the expected risk from case mix (without center effect) indicating a disparity among centers.

All analyses were performed using SAS Guide V7.1 (9.4) and R graphical packages from R 3.3.1 software.

Results

Study population

Females represented 23% of the 2347 candidates registered on the waiting list between 2010 and 2014 (Table 1). The mean age of the population was 51 ± 12 years. Most candidates were registered for dilated cardiomyopathy (46%) or coronary artery disease (36%) and presented varying degrees of severity of heart failure: 46% were in NYHA class IV, 20% were on inotropic support, 14% were on temporary mechanical circulatory support (MCS), and 8% were on long-term MCS. Some candidates presented renal or hepatic dysfunction (26% with glomerular filtration rate <50 ml/min/1.73 m^2 or on dialysis and 6% with bilirubin level ≥50 μmol/l).

During the 1-year postregistration period, 1525 (65%) candidates were transplanted, 263 (11%) died, 51 (2%) were delisted due to worsening of medical status, and 508 (22%) remained on the waiting list.

Center characteristics

Proportions of sensitized candidates, candidates with arrhythmias, candidates in intensive care unit (ICU) at registration, and class IV status candidates differed markedly from one center to another (Table 2, Fig. 2).

Heart donation rate in the DSA varied from 2.1 to 4.3 pmp. Four DSAs comprised three centers and the other three DSAs comprised two, three, and five centers. Two centers were considered to be attractive, as 45% of their candidates lived in another DSA. The donor heart offer decline rate ranged from 41% to 87%, and the lowest rate (41%) was observed in a center with a large candidate waiting list. The proportion of heart transplants procured from outside of the center's DSA ranged from 43% to 82%. About 20% of candidates were registered in one center, while the other candidates were equally distributed among the other 22 centers. The proportion of high-urgency candidates ranged from 17% to 56% between centers.

Factors contributing to 1-year access to transplantation

Women were transplanted more often than men (HR = 1.35 $P < 0.0001$) (Table 3). Blood group A or O candidates (0.77 and 0.64, respectively, versus group B; P-value <0.0001) and those with higher BMI (HR = 0.75 and 0.50 for BMI between 25 and 30 kg/m^2 and BMI ≥30 kg/m^2 versus lower BMI; P-value <0.0001) had lower access to transplantation. More severely ill candidates at the time of registration, that is, candidates in NYHA class IV (HR = 2.19 P-value <0.0001), candidates who were hospitalized (2.49 P-value <0.0001), and those treated with inotropic support (2.18 P-value <0.0001) were transplanted more often than other candidates. Temporary MCS was associated with better access to transplantation [HR = 2.50 (2.15–2.90)], in contrast with long-term MCS [HR = 0.93 (0.77–1.13)]. High serum bilirubin was also associated with better access to transplantation (HR = 1.95 P-value <0.0001).

The number of centers in the center's DSA, the proportion of hearts procured from outside of the center's DSA, and the number of candidates living in or outside the DSA were not factors associated with access to transplantation.

Finally, all candidate factors, except for glomerular filtration rate, were significant factors on multivariable analysis. Heart donation rate in the DSA (HR = 1.29; P-value <0.14) and the proportion of high-urgency candidates among listed patients (HR = 1.54; P-value <0.001) were associated with a higher risk of transplantation, whereas donor heart offer decline rate was significantly associated with lower access to transplantation (HR = 0.61; P-value = 0.001).

Between-center disparities

Among the 23 transplantation centers in France, seven had significantly better access and five had significantly lower access to transplantation (Fig. 3 Model 1).

After adjustment for candidate characteristics therefore slightly increased between-center variability by 5% (Fig. 3 Model 2), 11 centers were still situated outside of normal variability: five centers with better access and six centers with lower access, as the access of centers J, O, and R was no longer significantly different, while centers M and B were reclassified in the lower access group.

Additional adjustment for center characteristics decreased the between-center variability observed in Model 1 by 57% (Fig. 3 Model 3), access to transplantation of six centers became similar to that of the other

Table 1. Characteristics of candidates registered on the waiting list between 2010 and 2014 (N = 2347).

	Candidates *n* (%)	Missing data %
Blood group		
A	1037 (44)	–
AB	111 (5)	
B	273 (12)	
O	926 (39)	
Age (years) (mean, standard deviation)	51 (12)	–
Age (years)		
[18–54]	1305 (56)	
≥55	1042 (44)	–
Gender		
Male	1802 (77)	
Body mass index (kg/m^2)		
<25	1246 (53)	–
[24–29]	770 (33)	
≥30	331 (14)	
Sensitization		
No sensitization	1012 (43)	1.1
Sensitization	830 (35)	
At risk for sensitization*	505 (22)	
Indication		
Dilated cardiomyopathy	1070 (46)	–
Coronary artery disease	834 (36)	
Valvular cardiomyopathy	121 (5)	
Congenital heart disease	84 (4)	
Others	238 (10)	
NYHA class IV		
Yes	1088 (46)	2.3
Place of care		
At home	1202 (51)	0.7
Hospital or intensive care unit	1145 (49)	
Mechanical circulatory support (MCS)		
No MCS	1829 (78)	1.2
Temporary MCS†	335 (14)	
Long-term MCS‡	183 (8)	
Inotropic support		
Yes	470 (20)	2.1
High serum natriuretic peptide level§		
Yes	1340 (57)	12.3
Not applicable¶	526 (22)	
Pulmonary artery systolic pressure (mmHg)		
<41	705 (30)	7.1
≥41	1221 (52)	
Not done**	421 (18)	
Arrhythmia		
Yes	1141 (49)	
Glomerular filtration rate (MDRD) <50 ml/min/1.73 m^2		
No	1732 (74)	4.6
Yes	593 (25)	
Dialysis	22 (1)	
Bilirubin level (μmol/l)		
<35	1964 (84)	5.8
[35–50]	235 (10)	
≥50	148 (6)	
Prothrombin time (%)		
<50	124 (5)	6.8
[50–70]	381 (16)	
>70	747 (32)	
Vitamin K antagonist declined	1095 (47)	

MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; MDRD, Modification of the Diet in Renal Disease.

*At risk for sensitization = history of pregnancy, retransplantation, transfusion.

†Temporary MCS = balloon or ECMO.

‡Long-term MCS = total artificial heart or ventricular assist devices.

§High serum natriuretic peptide level = BNP > 400 pg/ml – ProBNP > 2000 pg/ml.

¶Not applicable for patients with MCS.

**Not done = catheterization was not performed for technical reasons.

centers, indicating that center characteristics can explain the differences initially observed in these centers. Differences in access to transplantation remained unexplained for five centers: two still had better access to transplantation and three still had lower access to transplantation.

Discussion

In the present study, we assessed between-center variability in access to heart transplantation in France and identified factors contributing to these disparities.

Although regional differences in terms of waiting time for heart transplantation have been recognized in France and the United States [9,22], previous studies have not clearly identified the factors explaining this regional variability. The strength of this study concerns the use of proportional hazard frailty models to simultaneously take into account the biases induced by the confounding effect generated by the different recipient case mix between centers, related to clustering of patients within centers and time to transplantation during the first year after registration.

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Table 2. Center characteristics ($N = 23$).

	Candidates *n* (%)	Number of centers
Heart donation rate in the center's DSA (pmp)		
<4	1977 (84)	20
≥4	370 (16)	3
Number of centers in the center's DSA		
≤4	1282 (55)	14
>4	1065 (45)	9
Proportion of candidates living outside the center's DSA among patients registered in the center (%)		
<17	1360 (58)	16
≥17	987 (42)	7
Center's donor heart offer decline rate (%)		
<80	1859 (79)	17
≥80	488 (21)	6
Proportion of hearts procured from outside of the center's DSA among hearts transplanted in the center (%)		
<70	1546 (66)	18
≥70	801 (34)	5
Number of candidates registered in the center		
≤110	1228 (52)	17
>110	1119 (48)	6
Proportion of HU candidates among candidates registered in the center (%)		
<50	1720 (73)	20
≥50	627 (27)	3

DSA, donation service area; HU, high-urgency status; Pmp, per million of population.

The unadjusted relative risk of transplantation within 1 year after registration varied considerably between centers, from 0.50 to 1.92. Several studies have reported geographic variations in access to kidney, liver, and heart transplantation in various countries [9–19]. Factors that could impact regional access to transplantation include differences in the populations requiring transplantation, differences in healthcare infrastructure supply or organization, as well as geographic variations in organ availability. This variability can also be attributed to the organ allocation system. In France, since 2004, heart allocation is primarily based on medical urgency: Donor organs are first offered to candidates at highest risk of waitlist mortality with nationwide organ sharing. Nevertheless, heart transplant allocation to nonpriority patients remains based on geographic criteria. During the study period, from January 2010 to December 2014, 53% of heart transplants were allocated according to the geographic model [23]. As the boundaries of DSA were defined without taking into account waiting list populations and heart donation rates, geography-based organ allocation has contributed to geographic variations in access to transplantation. The new heart allocation system currently being developed in France will expand nationwide organ sharing to nonpriority candidates.

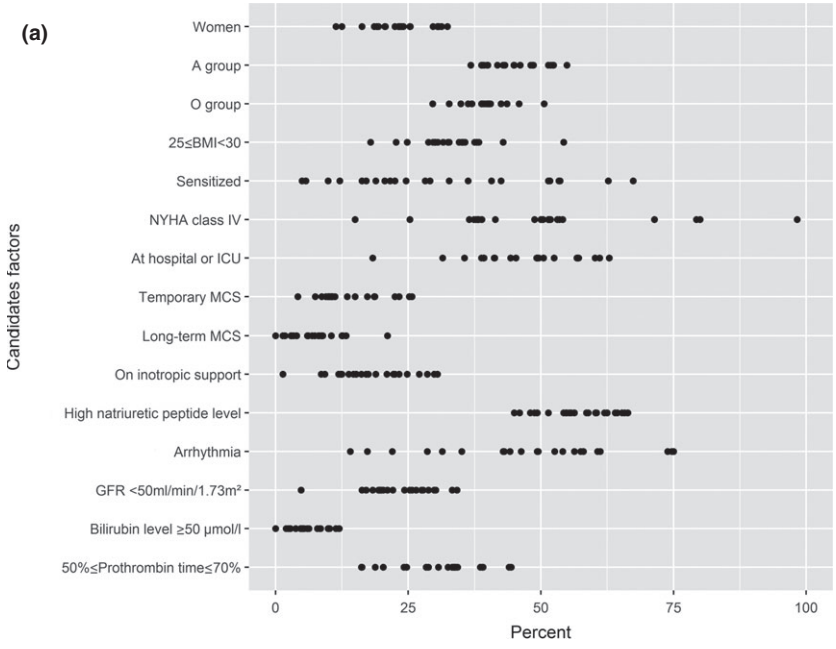
In line with a previous study from *Agence de la Biomédecine* [8], we identified, in the present study, 14 candidate characteristics predictive of 1-year access to transplantation. Two variables qualifying for priority status (inotropic support, short-term mechanical circulatory support), and seven variables related to heart failure severity and comorbidities (hospitalization, NYHA class IV symptoms, high serum natriuretic peptide level, arrhythmia, glomerular filtration rate, bilirubin level, prothrombin time) were associated with higher access to transplantation, while four variables related to candidate demographics (blood group O and A, age, male gender, increased body mass index) as well as candidate sensitization were associated with lower access to transplantation.

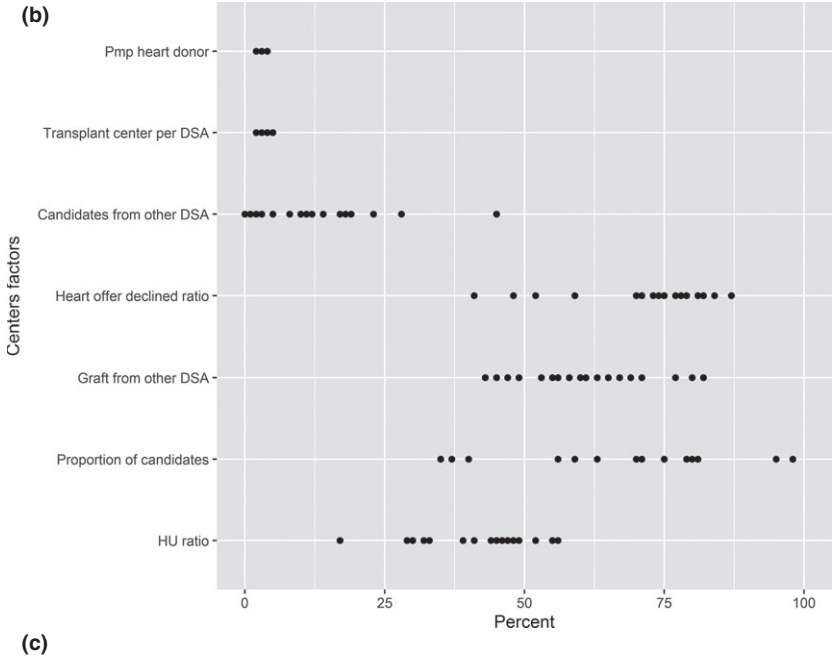
These factors were then analyzed across centers. Although the distribution of some of these factors differed between centers, between-center variability in access to transplantation remained unchanged after adjustment for these candidate characteristics.

The major finding of the study was that between-center variability in access to transplantation was mainly driven by three geographic factors (heart donation rate in the DSA, center heart offer decline rate, and proportion of high-urgency candidates among patients listed in the center), which accounted for 57% of all variability with a similar contribution for each factor.

A 2.4-fold variation in heart donation rates was observed between DSAs, ranging from 1.8 to 4.3 pmp. The current allocation system divides France into seven DSAs, each comprising two to five heart transplant centers. Access to transplantation, after adjustment for other center factors, was 29% higher in the DSA with the highest heart donation rate than in the DSA with the lowest heart donation rate. Of note, on multivariable analysis, the number of transplant centers per DSA and the number of patients newly listed per center did not impact access to heart transplantation.

Increased efficiency of the process could be a potential source of improvement, starting with identification of potential deceased donors and referral to the national transplant agency, particularly in DSAs with low heart donation rates. However, reduction of disparities in donation rates across DSAs will inevitably be limited by differences in population mortality rates. This limitation will be addressed by changing the allocation rules by broadening heart sharing for all candidates: The future score orienting heart to candidates rather than transplant teams could correct those geographic disparities.





(c)

DSA	Number of centers in the DSA	Heart donation rate in the DSA (pmp)
1	3	2.9
2	3	3.7
3	4	2.7
4	2	2.1
5	3	1.8
6	3	4.3
7	5	3

Figure 2 Graphical description of centers. (a) Distribution of candidate characteristics across centers. Each center is represented by one black circle. All *P*-values (chi-square test) were significant ($P < 0.05$) except for women and blood group. (b) Center characteristics. Each center is represented by one black circle. Percentage of candidates was the proportion of candidates in each center over the total number of candidates in France. Other indicators were the proportion in each center. (c) Donation service area (DSA) characteristics. Pmp, per million of population.

Table 3. Candidate and center risk factors associated with heart transplantation at 1 year: Univariate and multivariable Cox regression frailty models (N = 2347 registered on the cardiac waiting list between 2010 and 2014).

	Univariate with random effect on center			Multivariable with random effect on center (Model 3)		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Candidate factors						
Blood group						
A	0.77	0.66–0.90	<0.0001	0.75	0.64–0.87	<0.0001
AB	1.24	0.97–1.66		1.30	1.01–1.67	
B	1	–		1	–	
O	0.64	0.54–0.75		0.58	0.50–0.69	
Age (years)	0.99	[0.99–1.00]	<0.0001	1.00	[0.99–1.00]	0.1013
Gender						
Female	1.35	1.20–1.51	<0.0001	1.42	1.25–1.63	<0.0001
Male	1	–		1	–	
Body mass index (kg/m)						
<25	1	–	<0.0001	1	–	<0.0001
[24–29]	0.75	0.67–0.84		0.84	0.74–0.94	
≥30	0.50	0.42–0.59		0.53	0.45–0.63	
Sensitization						
No sensitization	1	–	<0.0001	1	–	<0.0001
Sensitization	0.64	0.57–0.73		0.56	0.49–0.64	
At risk for sensitization*	1.25	1.09–1.42		1.04	0.90–1.21	
NYHA class IV						
No	1	–	<0.0001	1	–	0.0004
Yes	2.19	1.96–2.43		1.28	1.12–1.46	
Place of care						
At home	1	–	<0.0001	1	–	<0.0001
Hospital or intensive care unit	2.49	2.24–2.77		1.59	1.36–1.87	
Mechanical circulatory support (MCS)						
No MCS	1	–	<0.0001	1	–	<0.0001
Temporary MCS†	2.50	2.15–2.90		1.45	1.11–1.90	
Long-term MCS‡	0.93	0.77–1.13		0.82	0.59–1.13	
Inotropic support						
No	1	–	<0.0001	1	–	<0.0001
Yes	2.18	1.93–2.47		1.52	1.28–1.80	
High serum natriuretic peptide level§						
No	1	–	<0.0001	1	–	0.0675
Yes	1.37	1.20–1.57		1.09	0.95–1.26	
Not applicable¶	1.97	1.70–2.31		1.40	1.05–1.86	
Arrhythmia						
No	1	–	0.02	1	–	0.0002
Yes	1.13	1.02–1.26		1.23	1.10–1.38	
Glomerular filtration rate (MDRD) <50 ml/min/1.73 m²						
No	1	–	0.25	1	–	0.1275
Yes	1.09	0.97–1.23		1.09	0.96–1.23	
Not applicable (dialysis)	0.74	0.35–1.57		0.57	0.27–1.20	
Bilirubin level (μmol/l)						
<35	1	–	<0.0001	1	–	0.0124
[35–50]	1.33	1.13–1.58		0.94	0.79–1.12	
≥50	1.95	1.59–2.38		1.34	1.09–1.65	
Prothrombin time (%)						
<50	1.55	1.22–1.97	<0.0001	1.33	1.05–1.69	0.1222
[50–70]	1.52	1.31–1.77		1.09	0.93–1.27	
>70	1	–		1	–	
Vitamin K antagonist	0.78	0.70–0.88		1.02	0.90–1.16	

Table 3. Continued.

	Univariate with random effect on center			Multivariable with random effect on center (Model 3)		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Center factors						
Heart donation rate in the center's DSA (pmp)						
<4	1	–	0.15	1	–	0.14
≥4	1.39	0.89–2.19		1.29	0.92–1.82	
Number of centers in the center's DSA						
≤4	1	–	0.45			
>4	1.13	0.81–1.58				
Proportion of candidates living outside the center's DSA						
<17	1	–	0.13			
≥17	1.30	0.93–1.82				
Center's donor heart offer decline rate (%)						
<80	1	–	0.0025	1	–	0.0006
≥80	0.61	0.44–0.84		0.61	0.46–0.81	
Proportion of hearts procured from outside of the center's DSA (%)						
<70	1	–	0.19			
≥70	1.29	0.88–1.88				
Number of candidates registered in the center (%)						
≤110	1	–	0.18			
>110	1.27	0.89–1.80				
Proportion of HU candidates (%)						
<50	1	–	0.07	1	–	0.013
≥50	1.51	0.97–2.35		1.54	1.09–2.18	

MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; MDRD, Modification of the Diet in Renal Disease; DSA, donation service area; HU, high urgency; CI, confidence interval.

The proportion of hearts procured from outside of the center's DSA was calculated among hearts transplanted in the center; the proportion of candidates living outside of the center's DSA among patients registered in the center and the proportion of HU candidates was calculated among candidates registered in the center.

The center effect was significant ($P < 0.0001$) after adjustment, as detailed in Fig. 3.

*At risk for sensitization = history of pregnancy, retransplantation, transfusion.

†Temporary MCS = balloon or ECMO.

‡Long-term MCS = total artificial heart or ventricular assist devices.

§High serum natriuretic peptide level = BNP > 400 pg/ml – ProBNP > 2000 pg/ml.

¶Not applicable to patients with MCS.

Changing the composition of population in each DSA is impossible but this study could also help the *Agence de la Biomédecine* in the mission of improving organ procurement by promoting the need for donors.

The heart offer decline rate varied among centers from 41% to 87% with a median of 75%. Access to transplantation, after adjustment for other center factors, was 39% higher in centers with the lowest heart offer decline rates than in centers with the highest heart offer decline rates. Apart from HU candidates, the French allocation system is based on rotation by transplant teams to ensure that organ offers are center-independent. Reported donor factors associated with heart decline include older donor age, female gender, cause of death, abnormal left ventricular ejection fraction, ventricular hypertrophy, abnormal valve function, abnormal coronary angiogram, hypertension, diabetes, cardiac arrest, high serum sodium, compromised donor history, and high catecholamine dose [15,24]. This list contrasts with the paucity of data showing an association between donor characteristics and post-transplant recipient survival. Interestingly, Khush *et al.* [15] reported a geographic variation in donor heart acceptance rates between regions in the United States, while predictors of heart decline were similar across UNOS regions. The authors underscored the need for evidence-based criteria for donor heart evaluation and acceptance for transplantation.

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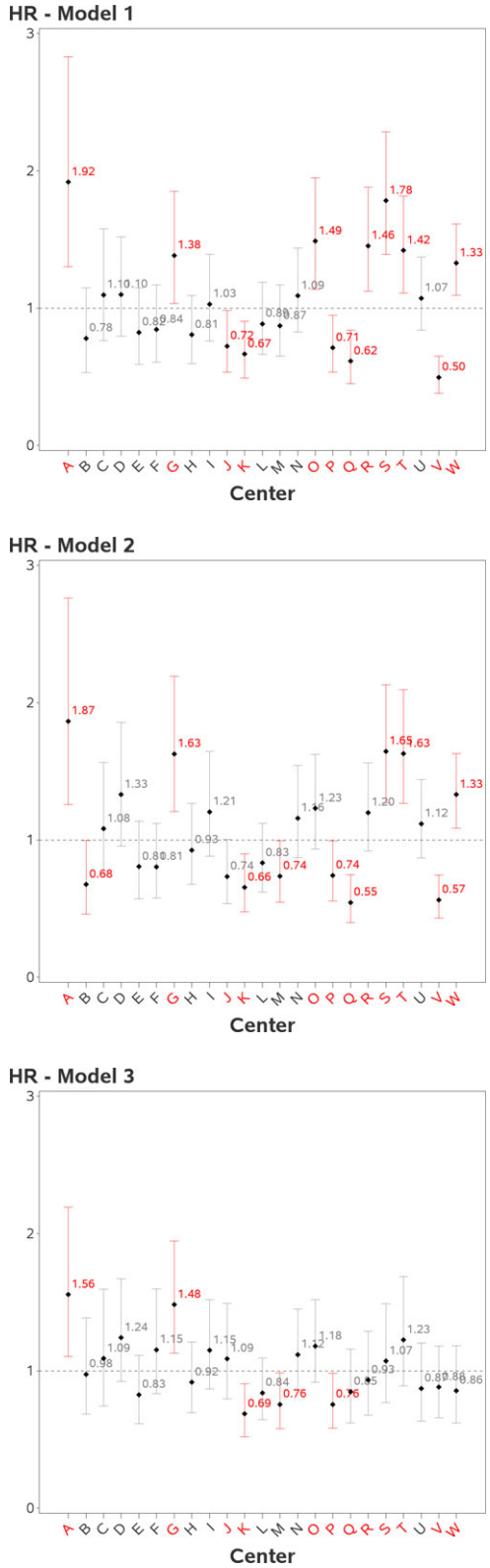

Figure 3 Unadjusted and adjusted relative risk of transplantation 1 year after registration on the heart waiting list (2010–2014). For each of three models, the individual prediction of the center effect on access to transplantation is expressed as a hazard ratio (HR): Centers with a HR > 1 (HR < 1) tended to access transplantation at a faster (lower) rate than the expected risk from case mix (without center effect) indicating a disparity among centers. Significant results are highlighted in red. Model 1: Random center effect alone. Center relative risks were unadjusted. Model 2: Random center effect adjusted for candidate factors. Center relative risks were adjusted for candidate factors: Adjustment included variables qualifying for priority status (inotropic support, short-term mechanical circulatory support), variables related to heart failure severity and comorbidities (hospitalization, NYHA class IV symptoms, high serum natriuretic peptide level, arrhythmia, glomerular filtration rate, bilirubin level, prothrombin time), and variables related to candidate demographics (blood group O and A, age, male gender, increased body mass index) as well as candidate sensitization. Model 3: Random center effect adjusted for candidate and specific-center factors. Center relative risks were adjusted for candidate and center factors: (i) Variables qualifying for priority status (inotropic support, short-term mechanical circulatory support), variables related to heart failure severity and comorbidities (hospitalization, NYHA class IV symptoms, high serum natriuretic peptide level, arrhythmia, glomerular filtration rate, bilirubin level, prothrombin time), and variables related to candidate demographics (blood group O and A, age, male gender, increased body mass index) as well as candidate sensitization as candidate factors. (ii) Heart donation rate in the DSA (pmp), rate of HU candidates, and donor heart offer decline rate as center factors.

The percentage of high-urgency status patients varied among centers from 17% to 56% with a median of 41%. Access to transplantation, after adjustment for other center factors, was 54% higher in centers with the highest percentage of high-urgency status patients than in centers with the lowest percentage. As the allocation system effectively prioritizes candidates, the criteria for access to priority status should be objective, accurate, and transparent. In France, as in many countries around the world, the organ allocation system is based on medical urgency, primarily defined by medical management. The current allocation system is therefore dependent on the healthcare provider's description of treatment options and is not based on objective data. This system may create between-center disparities in access to transplantation in patients with similar risk of waitlist mortality. In this context, a new heart allocation system is currently being developed in France, based on a candidate risk score including two markers of heart failure severity and two markers of end-organ dysfunction [25].

Although a large proportion of the variability was explained by center factors identified in the CRISTAL database, studies on outliers may help to elucidate the remaining factors responsible for these disparities, for instance, center-specific policies, such as nursing staff.

These findings were discussed with the working group composed by professional (and representatives of the transplant centers) dedicated on the general

evaluation process, which leads to changing heart allocation in France. To go further, the use of hospital database could help to carry out qualitative study on the organization and functioning of these outlier centers replaced on a hospital context (medical staff dedicated to transplantation, technical and logistical organization).

This study presents several limitations. It was based on analysis of data collected in a national registry, comprising missing data and data subject to coding errors. However, the CRISTAL database is a high-quality database comprising repeated quality controls. Variables not available in the database and not taken into account in the analyses may impact the between-center variability in access to transplantation, such as differences in candidate socioeconomic status and institutional resources and practices. Of note, the French healthcare system is a universal system, thereby reducing the consequences of poor social policy in contrast with the United States healthcare system [26].

In addition, our evaluation of the demand for heart transplantation was limited to the number of candidates newly listed without considering the regional incidence of advanced heart failure or the transplant center referral rate.

Finally, the donor offer decline rate is center-dependent, as observed by Khush in the United States [15]. We analyzed heart offers that were refused by one center but finally accepted by another team, reflecting different donor selection criteria between centers. Organ acceptance practices may depend on the center's experience and expertise in managing problems associated with marginal organs. Several studies have reported favorable post-transplant survival using marginal hearts [27,28]. Post-transplant outcomes were not taken into account in this study but are currently assessed by the *Agence de la Biomédecine* using a funnel plot of 1-year post-transplant outcomes per center adjusted for recipient characteristics [29]. The funnel plot results of patients transplanted between 2010 and 2013 can be compared to those of this study. Centers with lower or higher access to transplantation were not those detected as outliers in funnel plot with an increased 1-year adjusted risk of graft failure or death. Organ acceptance practices may also depend on the organization and management of resources, which could be investigated by more detailed quantitative studies.

In conclusion, a multilevel model introducing a center random effect was used to demonstrate whether a significant variation persisted between centers after risk adjustment for both candidate and center factors. The mixed-effect Cox model accounts for survival time to transplantation and clustering, taking into account correlation between patients in the same center. We were enabled to quantify the among center variability and quantify the amount of variability explained by patient or center variables. As individual characteristics are globally constant across centers despite differences in medical care, the geographic differences detected reflect disparities in access to transplantation [19] induced by the current organ allocation system.

The main center factors were the heart donation rate in the Donation Service Area (DSA) (pmp), the proportion of HU candidates, and the donor heart offer decline rate. These factors are mediated by the clinical severity of candidates, the allocation system, and registration practices rather than by transplant activity [30]. In collaboration with all stakeholders, the French national transplantation agency is currently developing a new organ allocation system to reduce these disparities, by basing allocation on candidate characteristics (severity of heart failure, post-transplant survival) rather than center characteristics.

Authorship

CC: study concept and design, statistical analysis, interpretation of result, writing of the manuscript, study supervision. RD: study concept and design, interpretation of result, writing of the manuscript. ES: critical of the statistical analysis, critical revision of the manuscript. PT: study concept and design, interpretation of results, critical revision of the manuscript. GL: critical revision of the manuscript. CL: study concept and design, critical of the statistical analysis, interpretation of results, writing of the manuscript. OB: critical revision of the manuscript, study supervision.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgements

We would like to thank the technicians involved in the clinical studies and those who entered data into the database.

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