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Pediatric marginal donor hearts: Trends in US national use, 2005-2014

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Abstract

Pediatric patients awaiting heart transplant face high mortality rates due to donor organ shortages, including non-use of marginal donor hearts. We examined national trends in pediatric marginal donor heart use over time. UNOS data were queried for heart donors <18 years from 2005 to 2014. The proportion of donor hearts considered marginal was determined using previously cited marginal characteristics: left ventricular ejection fraction (LVEF) <50%, use of ≥2 inotropes, cerebrovascular death, CDC high-risk status, and eGFR < 30 mL/min/1.73 m^2. Disposition of donor hearts was determined and stratified by marginal donor status. Of 6778 pediatric hearts offered from 2005 to 2014, 2373 (35.0%) were considered marginal. Non-use of marginal donor hearts was significantly higher than that of donor hearts without any marginal characteristics (59.5% vs 20.3%, $P < .001$). In particular, LVEF < 50% and donor inotropes were associated with high rates of organ non-use among pediatric donors. Yet, non-use of marginal donor organs decreased from 67% to 48% from 2005 to 2014 ($P < .001$). Although the proportion of pediatric donor hearts used for pediatric patients has increased, more than half of donor hearts are declined for use in pediatric recipients due, in part, to perceived marginal status.

KEYWORDS

cardiac, donor, heart, marginal, pediatric, transplant

1 | INTRODUCTION

Heart transplantation remains the therapeutic gold standard for symptomatic heart failure refractory to medical management in the pediatric population. Children awaiting heart transplant face the highest waitlist mortality of any cohort awaiting solid organ transplant in the United States, with death rates reported around 8%-17%.[1,2] Among those less than 1 year of age, approximately 1 in 4 infants will die annually awaiting heart transplantation.[3,4] With no readily identifiable new source of donor hearts, there is significant benefit to ensuring maximal use of available donor hearts.

A key reason for donor non-use is the concept that some donor hearts exhibit "marginal" characteristics—ill-defined physiologic, demographic, or social characteristics that may increase risks associated with transplantation. Up to one-third of all adult donor hearts are not used, largely ascribed to avoidance of marginal characteristics.[5] However, some adult transplant centers, faced with a growing shortage of donor organs, have demonstrated good transplant

Abbreviations: CDC, Centers for Disease Control and Prevention; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

outcomes with variably defined "marginal" donors.[6,7] Similarly, in the pediatric population, multiple studies in recent years have found variable impact on outcomes based on potentially marginal donor criteria including donor inotrope use, need for CPR, mechanism of death, troponin level, CDC high-risk status, or donor-recipient weight mismatch.[8-12] The single donor variable that has been associated with poor transplant outcome is donor ejection fraction, but this finding is inconsistent as well.[13,14] Despite the lack of clear evidence, these potentially marginal characteristics continue to be associated with non-use of pediatric donor hearts.[15]

In the absence of compelling evidence that such hearts confer increased risk, understanding programs' reluctance to use potentially marginal donor hearts may help to maximize the utilization of a broader pool of donor hearts for children awaiting transplantation. Khan and colleagues recently elucidated the characteristics associated with pediatric donor heart non-use, which provides insight into how pediatric transplant programs may internally define a marginal organ. To better understand the changing views on donor selection criteria, this study seeks to demonstrate trends in pediatric donor heart utilization over the last decade, with special attention to these potentially marginal donors.

2 | METHODS

2.1 | Study design and patient sample

This study was a retrospective analysis of pediatric heart transplant data from the UNOS registry and was deemed exempt by the Institutional Review Board at Nationwide Children's Hospital.

The UNOS registry was queried for all deceased pediatric (age < 18 years) donor hearts available for possible transplantation between 2005 and 2014. Available donor hearts were assigned marginal status if at least one of the following criteria was met as follows: (i) LVEF of donor heart <50%; (ii) donor identified as CDC high-risk status; (iii) CVA or stroke listed as primary etiology of donor death; (iv) donor GFR <30 mL/min per 1.73 m^2; or (v) donor was on at least 2 inotropic agents at time of death.[5,15] Inotropic agents evaluated were dobutamine, dopamine, epinephrine, norepinephrine, and phenylephrine. By defining "marginality" based on factors associated with non-use, we sought to assess current practices in donor organ use and the impact of prior research on current clinical practice. We disregarded other criteria, such as non-O blood type and age >1 year, which were likely sequelae of the organ allocation process. Other characteristics classically thought to be "marginal" such as prolonged CPR or downtime were not included as these data were not available in the UNOS database.

2.2 | Main study outcome

The primary study outcome was final disposition of available donor hearts, classified as: (i) not accepted for transplantation; (ii) transplanted to adult recipient; (iii) transplanted to pediatric recipient; or (iv) transplanted, yet with recipient age unknown. The

TABLE 1 Final disposition of deceased pediatric donor hearts reported to the UNOS between 2005 and 2014

	Total, n (%)	Heart not accepted for transplant	Heart transplanted in adult recipient	Heart transplanted in pediatric recipient	Heart transplanted, unknown recipient age
All available deceased donor hearts between 2004 and 2014[a], n (%)	6778	2306 (34.0%)	1510 (22.3%)	2860 (42.2%)	102 (1.5%)
Donor hearts with none of the marginal criteria[b], n (%)	4405 (65.0%)	893 (20.3%)	1207 (27.4%)	2233 (50.7%)	72 (1.6%)
Donor hearts with ≥1 marginal criteria[b], n (%)	2373 (35.0%)	1413 (59.5%)	303 (12.7%)	627 (26.4%)	30 (1.3%)
LVEF < 50%	1354 (20.0%)	1155 (85.3%)	60 (4.4%)	130 (9.6%)	9 (0.7%)
CDC high risk	328 (4.8%)	114 (34.8%)	83 (25.3%)	126 (38.4%)	5 (1.5%)
CVA/stroke as donor etiology of death	422 (6.2%)	175 (41.5%)	72 (17.1%)	170 (40.3%)	5 (1.2%)
Donor GFR ≤ 30 mL/min per 1.73 m^2	484 (7.1%)	165 (34.1%)	102 (21.1%)	207 (42.8%)	10 (2.1%)
Donor on ≥ 2 inotropic agents[c] at time of death	227 (3.3%)	152 (67.0%)	22 (9.7%)	50 (22.0%)	(1.3%)

[a]Only deceased donor hearts with complete data to assess donor marginal status were included in study sample.
[b]Marginal criteria were defined as follows: (i) donor heart having LVEF < 50%; (ii) donor classified as CDC high risk; (iii) CVA or stroke identified as primary etiology of donor death; (iv) donor having GFR ≤ 30 mL/min per 1.73 m^2; and (v) donor on ≥2 inotropic agents at time of death. Donor hearts could meet more than 1 marginal criterion.
[c]Inotropic agents of interest included the following: dobutamine, dopamine, epinephrine, norepinephrine, and phenylephrine.

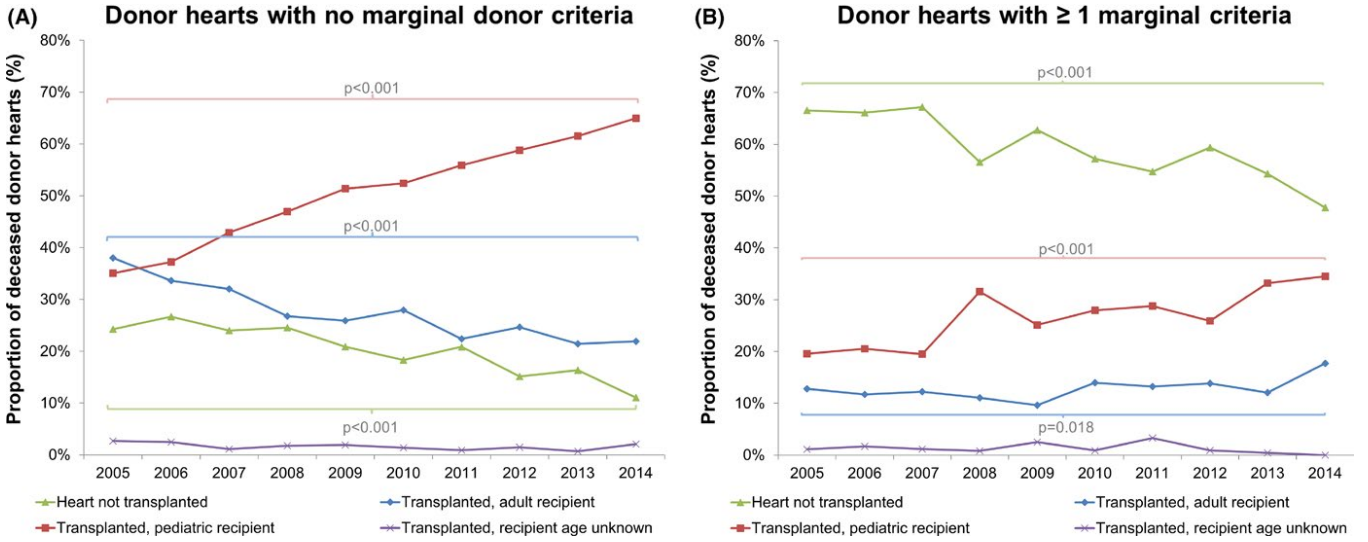

FIGURE 1 Final disposition of pediatric donor hearts available between 2005 and 2014, classified by marginal donor heart status

final study sample included all available pediatric donor hearts for which marginal donor status and final disposition could be determined.

2.3 | Statistical analyses

The proportion of available pediatric donor hearts identified to be of marginal donor status was determined, as well as the proportion of donor hearts meeting each marginal donor criterion. Among donor hearts considered to be of marginal donor status, the proportions not accepted for transplant vs transplanted in recipients of different ages were calculated for each calendar year. This analysis was repeated for donor hearts that met none of the marginal donor criteria. Linear trends over time in the primary study outcome, separated by marginal donor status, and then by each of the individual marginal criteria, were assessed using the Cochran-Armitage test for trend. Finally, to evaluate if the disposition of donor hearts varied by marginal donor criteria, we calculated the proportion of donor hearts not accepted vs transplanted that met each marginal criterion. Data analyses were performed using Stata 12.1 (StataCorp, LP, College Station, TX, USA) with a *P*-value < .05 considered statistically significant.

3 | RESULTS

There were 6778 pediatric donor hearts available between 2005 and 2014, of which 2306 (34%) were not harvested for transplantation, and only 2860 (42%) were transplanted to pediatric recipients (Table 1). Of the donor hearts with ≥1 marginal characteristic, 59.5% (n = 1413/2373) were not used, compared to 20.3% (n = 893/4405) of the hearts with none of the marginal criteria (*P* < .001). The rates of non-use of donor hearts ranged from 34.1% to 85.3%, depending on the specific marginal criteria evaluated. Donor hearts on ≥2 inotropic agents at the time of death or having an LVEF < 50% had the highest rates of non-use (Table 1). Of the 2860 pediatric donor to pediatric recipient transplants performed over the study period, 627 (21.9%) were recovered from donors who met one or more of our criteria for marginality.

Overall, pediatric donor heart to pediatric recipient transplantation increased from 28.8% to 54.4% from 2005 to 2014 (*P* < .001). Figure 1 shows national trends in use of pediatric donor hearts over time, classified by marginal donor heart status. Among pediatric donor hearts with none of the marginal donor criteria, the proportion recovered for transplantation in pediatric recipients increased from 35.1% to 65.0% from 2005 to 2014 (*P* < .001), with corresponding decreases in proportions of pediatric hearts used for adult recipients or not used (*P* < .001 for both linear trends). From 2005 to 2014, use of pediatric donor hearts considered marginal in pediatric recipients increased significantly from 19.6% to 34.5% (*P* < .001), while the proportion of marginal donor hearts not used decreased from 66.5% to 47.8% (*P* < .001). Over the same time period, use of pediatric marginal donor hearts in adult recipients did not change significantly (*P* = .11).

Table 2 presents differences in use of marginal donor hearts for transplantation by specific marginal criteria. Having an LVEF < 50% was the most common criteria leading to classification as marginal donor status (n = 1354/2373; 57.1%) and was most prevalent among marginal hearts not accepted for transplant (n = 1155/1413; 81.7%). However, among marginal donor hearts that were transplanted, there were no differences in the breakdown of specific marginal criteria (Table 2).

Lastly, Figure 2 presents trends in the proportion of donor hearts that were used for transplantation in pediatric recipients, stratified by each of the marginal criteria studied. The use of hearts considered to be CDC high risk or from donors who died of CVA/stroke increased over the study period, while hearts meeting the other criteria did not have significant changes in utilization over time.

TABLE 2 Differences between deceased donor hearts considered marginal and were transplanted vs not accepted for transplant between 2005 and 2014

	All available deceased donor hearts considered marginal (n = 2373)	Heart not accepted for transplant (n = 1413)	Heart transplanted (n = 960)
LVEF < 50%	1354 (57.1%)	1155 (81.7%)	199 (20.7%)
CDC high risk	328 (13.8%)	114 (8.1%)	214 (22.3%)
CVA/stroke as donor etiology of death	422 (17.8%)	175 (12.4%)	247 (25.7%)
Donor GFR ≤ 30 mL/min per 1.73 m^2	484 (20.4%)	165 (11.7%)	319 (33.2%)
Donor on ≥ 2 inotropic agents at time of death	227 (9.6%)	152 (10.8%)	75 (7.8%)

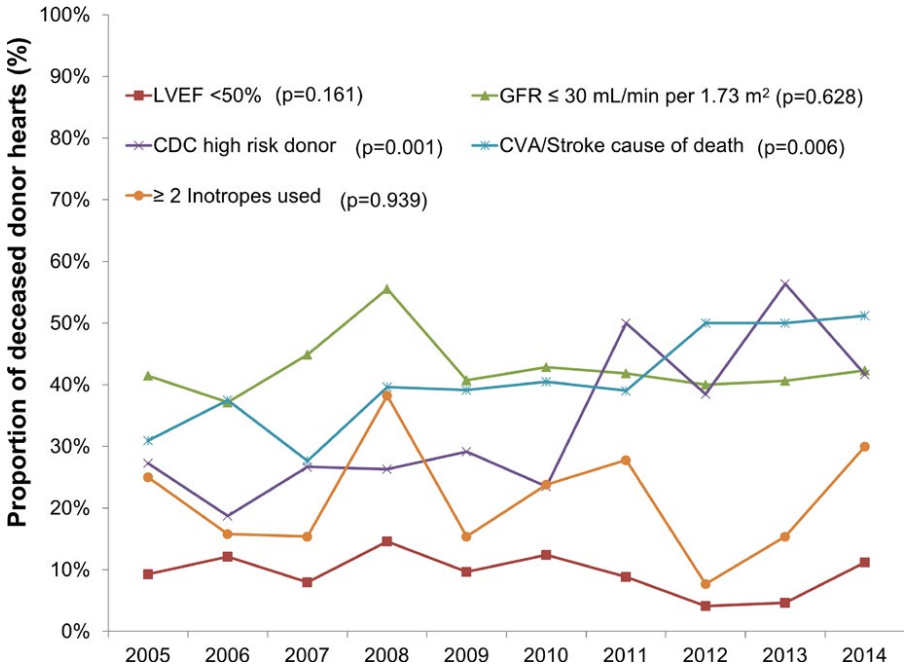

FIGURE 2 Marginal donor heart use in pediatric transplant recipients from 2005 to 2014, separately by each marginal donor criterion. *P*-values for linear tests of trend over time for each criterion are presented in the legend

4 | DISCUSSION

Our analysis demonstrates that the proportion of pediatric donor hearts used in pediatric recipients has nearly doubled from 2005 to 2014, driven not only by increased use of hearts without marginal characteristics, but also to some extent by increased use of potentially marginal donor hearts. Nevertheless, while there has been a national trend over time toward greater use of donor hearts with marginal characteristics, as of 2014, close to half of these hearts were still not being used for transplantation. Donor hearts with an LVEF < 50% was the most common criteria associated with marginal donor classification and non-use for transplantation. Importantly, our analysis demonstrates that among donor hearts meeting none of the commonly cited marginal criteria, up to one-third were not being used in pediatric candidates in 2014.

Pediatric patients awaiting heart transplant have high mortality driven in part by long wait times for suitable donor organs. Thus, there has been renewed interest in understanding factors driving acceptance of donor organs to maximize the use of pediatric donor organs and to better define donor characteristics that may predict poor transplant outcomes with more certainty.[14] With the lack of reproducible data examining donor heart quality, characterization of marginality in donor hearts is controversial and likely varying across institutions. In an effort to be comprehensive, the "marginal" donor definition used in our analysis was derived from prior work describing characteristics highly associated with pediatric donor heart non-use, including LVEF < 50%, CDC high-risk status, use of inotropes, cerebrovascular cause of death, and donor eGFR.[5,15-17] It is important to note that prior studies have not consistently demonstrated that these individual characteristics have a significant impact on pediatric heart transplant outcomes, defined specifically by 1-year post-transplant survival.[10,12,13] Recently, Conway et al did not find any impact of cerebrovascular cause of death on post-transplant outcomes, whereas Bailey et al showed no difference in outcomes with donor hearts previously declined due to quality.[8,10] However, data assessing LVEF as a predictor of

outcomes are conflicted as Zafar and colleagues found a decrease in 1-year mortality, while Rossano et al[13,14] found no significant difference in graft survival stratified by LVEF. However, despite the continued lack of evidence of poor outcomes based on donor organ quality alone, we demonstrate that these potentially marginal characteristics continue to have significant contribution to the non-use of donor organs.

Despite a large number of pediatric hearts still not being used for transplantation, a promising finding was an increase in use of marginal and non-marginal donor hearts in children during the study period. This suggests a shift in practice by pediatric transplant cardiologists to address organ shortages and willingness to accept donor organs that previously would be considered marginal, or less than ideal. As expected, due to long-standing practice, the rate of marginal donor heart use is increasing at a slower rate compared to non-marginal. Our analysis shows that the vast majority of the marginal hearts not being used had poor functional criteria, including low LVEF or higher inotropic support. In addition, we found that there has been no change in utilization of donor organs with an LVEF < 50% over the study period. Instead, the increased use of marginal donor hearts in children appears to be at least partially driven by acceptance of donor hearts meeting other marginal criteria that are not associated with left ventricular function, such as CDC high-risk status or non-cardiac donor causes of death.

With no age restriction for acceptance of organs from a pediatric donor, marginal pediatric donor hearts are used with regularity in adult candidates. Zafar and colleagues reported excellent outcomes associated with adolescent donor hearts declined by pediatric centers that were ultimately transplanted at adult centers.[18] Our analysis found that 22% of the pediatric donor hearts are eventually used for transplantation in adult recipients. While these donors were likely of larger size and there may have been potentially fewer adolescent pediatric candidates waitlisted at the time those donors were available, up to 1500 additional pediatric transplants may have been performed over 10 years had those hearts been used for pediatric candidates. Maximizing pediatric adolescent donor heart use within the pediatric population is one avenue to reduce pediatric waitlist mortality and wait times.

Lastly, with only tentative evidence demonstrating an association between marginal donor characteristics and poor transplant outcomes, it remains perplexing that so many potential donor hearts were never used over the entire study period—a third of all donors were not used. Strikingly, when focused on hearts with none of the marginal criteria we used in this analysis, 13% of potentially "perfect" pediatric donor hearts were never used for transplant, adult or pediatric. While other criteria such as specific patient needs regarding distance, size, and allosensitization may have contributed to the non-use of these donor organs, these organs represent almost 900 missed opportunities for viable pediatric transplants. Further research into the decision process and biases underlying donor organ acceptance is required, so as to ensure that these decisions are made based on our best understanding of potential donor risk factors.

4.1 | Limitations

While this study attempts to leverage a national registry, there are several limitations to this retrospective database review. In particular, as our definition of a marginal donor was empirically derived from factors associated with non-use and commonly cited as marginal, the cohort of marginal donors also reflects institutional and practitioner biases, which could not be further delineated with the available data. Furthermore, as the dataset analyzed does not contain data regarding the offers made to potential accepting centers, we cannot determine rates of organ acceptance by center. Lastly, due to the retrospective study design of our analysis, we cannot account for data entry errors and potential influential variables not included in the registry.

5 | CONCLUSION

With no new expansion in the available donor pool in the foreseeable future, it will be important to modify our definition of what constitutes a marginal donor organ based on the available literature in the pediatric population. Increased willingness to utilize organs with marginal characteristics previously shown to have no effect on outcome will allow pediatric centers to offer more hearts to those in need. Moreover, understanding the non-use of donor organs without identifiable marginal criteria is necessary to improving organ usage. With the increasing use of organs with and without marginal characteristics, further studies are needed to evaluate center and regional variability in donor acceptance practices, post-transplant outcomes using donors with marginal characteristics, and characterize donor organ characteristics that are more accurately predictive of unacceptable outcomes.

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CONFLICT OF INTEREST

None of the authors listed on this manuscript has a financial relationship with a commercial entity that has an interest in the subject matter of the presented manuscript or other conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Adam K. Morrison: Concept/Design, data analysis/interpretation, drafting article, critical revision of article, and approval of article; Charitha Gowda: data analysis/interpretation, drafting article, critical revision of article, approval of article, and statistics; Dmitry Tumin: data analysis/interpretation and statistics; Christina Phelps: critical revision of article and approval of article; Don Hayes, Jr.: critical revision of article and approval of article; Joseph Tobias: Critical, revision of article and approval of article; Robert Gajarski: Concept/Design, data interpretation, drafting article, critical revision of article, and approval of article; Deipanjan Nandi: Concept/Design, data analysis/interpretation, drafting article, critical revision of article, approval of article, and statistic.

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