




“Take it or leave it”: Analysis of pediatric heart offers for transplantation in Switzerland

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Abstract

Background: There is a shortage of donor hearts in Switzerland, especially for pediatric recipients. However, the rate and reason for refusals of pediatric donor hearts offered in Switzerland has not been systematically analyzed.

Methods: The national transplant database, Swiss Organ Allocation System, was searched for all hearts from Swiss and foreign donors younger than 16 years from 2015 to 2020. The numbers of accepted and refused hearts and early outcome were assessed, and the reasons for refusal were retrospectively analyzed.

Results: A total of 136 organs were offered to the three Swiss pediatric heart centers and foreign donor procurement organizations. Of these, 26/136 (19%) organs were accepted and transplanted: 18 hearts were transplanted in Switzerland, and 13 of these were foreign. Reasons for refusal were (1) no compatible recipient due to blood group or weight mismatch, 89.4%; (2) medical, meaning organ too marginal for transplantation, 7.4%; (3) logistic, 1.4%; and (4) other, 1.8%. Five organs were refused in Switzerland by one center but later accepted and successfully transplanted by another center. Hearts from outside Switzerland were transplanted significantly less than Swiss hearts ($n = 16/120$ vs. $10/16$, $p < .001$).

Conclusion: The most common reason for refusing a pediatric donor heart is lack of compatibility with the recipient. Few hearts are refused for medical reasons. A more generous acceptance seems to be justified in selected patients. Switzerland receives a high number of foreign offers, but their rate of acceptance is lower than that of Swiss donations.

KEYWORDS

donor rejection, donor selection, pediatric heart transplantation

Abbreviations: CPR, cardiopulmonary resuscitation; ISHLT, International Society for Heart and Lung Transplantation; LVEF, left ventricular ejection fraction; SOAS, Swiss organ allocation system.

Stéphane Maire and Martin Schweiger have contributed equally to this work.

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1 | INTRODUCTION

A shortage of suitable heart donor organs has resulted in relatively long waiting times and high waitlist mortality. In Switzerland, the average waitlist mortality is 17.4%.¹ However, not all organs that are offered for transplantation can be allocated to a recipient. In Switzerland, between 2007 and 2013, only 27.5% of all the adult and pediatric donor hearts offered were transplanted.¹ Detailed data of the pediatric heart transplantation allocation process in Switzerland has not been published so far.

Donor characteristics such as left ventricular ejection fraction (LVEF) <50%,^{2,3} need for cardiopulmonary resuscitation (CPR),⁴ and height mismatch⁵ have to be considered before accepting organs for heart transplantation. However, studies have shown conflicting results concerning these risk factors.⁶⁻⁸ Moreover, donor organs that were refused due to their quality by one center but eventually accepted elsewhere produced no increase in mortality in recipients who eventually received them.^{9,10}

The refusal of acceptable donor offers which have been transplanted eventually is associated with higher waitlist mortality without improved post-transplant outcome.¹¹ Therefore, further investigation of risk factors and decisions during the allocation process may help to reduce waiting times and waitlist mortality.

The aim of our study was to investigate the rationale for refusing and/or accepting donor hearts in children in Switzerland. Furthermore, we wanted to investigate whether the reasons for refusal were in line with current recommendations and guidelines.^{12,13}

2 | METHODS

2.1 | Study cohort

For this retrospective study, the Swiss organ allocation system (SOAS) data was searched for all hearts from pediatric donors, those less than 16 years of age, between 01.07.2015 and 31.08.2020. All Swiss and foreign hearts offered were included in this study. Offers were excluded if they had been withdrawn by the Swiss National Foundation for Organ Donation and Transplantation (Swisstransplant) or a foreign organ procurement organization. For each offer, all pediatric patients, those less than 16 years of age, that were on the SOAS waitlist at the time of the offer were included as potential recipients. Because every pediatric organ is offered primarily to a pediatric recipient, even though it may later be allocated to an adult recipient, we also included donor organs that were finally allocated to an adult recipient in our cohort.

2.2 | SOAS database contents

Offers from Swiss donors are registered in SOAS and allocated by an algorithm that creates a priority list of potential recipients on the waitlist.¹ If a center refuses an offer, the reason for refusal is entered

in SOAS in one of four categories: (1) noncompatible recipient, due to blood group, size, or weight mismatch; (2) medical, such as that the organ is too marginal for transplantation due to low LVEF or donor infection; (3) logistic, due to distance or unavailability of a surgical team; or (4) other. If all transplantation centers refuse the offer, the offer is passed on to foreign organ procurement organizations. The reasons for refusal from Swiss donors in foreign countries are not registered in SOAS and not part of this study. Offers from foreign organ procurement organizations are registered in SOAS and transmitted to all Swiss transplantation centers. If all Swiss centers refuse a foreign organ offer, Swisstransplant no longer monitors the process; therefore, it is unknown whether the organ was finally accepted and transplanted in another country. We noted for all Swiss and foreign offers whether the offer was accepted and transplanted or whether the offer was refused and which reasons were given in Switzerland. Reasons with the comment "for all centers" in SOAS were counted once for each pediatric heart transplantation center in Switzerland: Bern, Lausanne, and Zurich. If multiple reasons were given for refusal, only the main reason was defined and included in the study after individual review of all available clinical details.

2.3 | Patient characteristics

The following donor characteristics were collected: age, sex, country of donor origin, blood group, LVEF, renal function, duration of cardiopulmonary resuscitation, and viral serology. Inotropic use was defined as any administration of dobutamine, dopamine, norepinephrine, or adrenalin after admission to the hospital. The causes of donor brain death were categorized as (1) cerebral trauma, (2) cerebral hemorrhage without trauma, (3) cerebral disease such as cerebrovascular insult (4) anoxia, for instance due to drowning, or (5) other cause, for example meningitis.

The following Swiss recipients' characteristics were analyzed: age, weight, sex, blood group, diagnosis, ischemic time, waitlist time, donor-recipient weight ratio, mechanical circulatory support before transplantation, and virtual cross-match. Foreign recipients were not included in the analysis.

2.4 | Subgroup analyses

For all refused organ offers, we retrospectively simulated the allocation process by comparing the donor and potential recipient characteristics on the waitlist using three criteria: (1) donor-recipient weight ratio, (2) donor LVEF, and (3) donor-recipient ABO blood group compatibility. The acceptable reference ranges within the three criteria were first set to traditional commonly applied values and then extended to a less strict definition as recently proposed by the consensus statement on donor acceptability of the International Society for Heart and Lung Transplantation (ISHLT).^{12,13} (1) Donor-recipient weight ratio: traditional criteria 0.8–2.0, extended criteria 0.6–3.0; (2) Donor LVEF: traditional criteria LVEF >50%, extended

criteria: LVEF >40%; and (3) ABO blood group compatibility: traditional criteria ABO compatible only, extended criteria for recipients younger than 2 years of age, all types of ABO blood groups; for recipients older than 2 years of age, ABO compatible organs only.

For all accepted offers, we examined whether another center had refused the offer for other reasons than donor–recipient weight ratio outside of 0.8–2.0 or ABO incompatibility. These cases were analyzed individually for the reasons for refusal, the characteristics of the donor and potential recipient, and the current recommendations. Survival was collected from the recipient's records at the transplantation center.

2.5 | Statistical analysis, ethics, and data protection

Donor characteristics from refused and accepted organs were compared using Pearson chi-squared and Fisher's exact tests for categorical variables. For continuous variables, Mann–Whitney *U*-test was used. Statistical analysis was performed using IBM SPSS Statistics 28.0.1.1; tables and graphs in Microsoft Excel 2007. The study was approved by the ethical committee (BASEC-Nr. 2021-00833). All parents or guardians signed an informed consent before registration to SOAS. All data were analyzed pseudonymously.

3 | RESULTS

3.1 | Donor characteristics

Between 01.07.2015 and 31.08.2020, 136 pediatric donor heart offers met the inclusion criteria for our study. Donor characteristics are shown in detail in Table 1. The majority ($n=120$; 88.2%) of pediatric organs offered in Switzerland were procured from donors of foreign countries. The foreign hearts originated from France ($n=50$), Germany ($n=16$), Spain ($n=11$), and 14 other countries ($n=43$). The majority of foreign hearts were refused (86.7%) while Swiss hearts were less often refused (37.5%; see Figure 1). The proportion of Swiss donors was higher among the accepted hearts than among the refused hearts (Table 1). Seven offers were accepted from donors after a resuscitation of more than 20 min, five of them between 20 and 60 min, and two of them over 60 min. One of these last two hearts was initially refused due to prolonged resuscitation time but later successfully transplanted. No donors had HIV, hepatitis B virus or hepatitis C virus positive serology (not shown in Table 1).

3.2 | Recipient characteristics

The characteristics of the 18 recipients who were transplanted in Switzerland are shown in Table 2. In three of the foreign organs, a Swiss and a foreign center were interested at the same time, and the organ was eventually accepted outside Switzerland. For each heart

offered, a median of 2 (range 1–5) potential recipients had been on the pediatric waitlist in Switzerland. Of the 26 accepted organs, two resulted in a donor–recipient weight ratio higher than 2.0 and four smaller than 0.8. The largest donor–recipient weight ratio in our cohort was 3.4. The donor was a 9-month-old child whose heart was transplanted into a 1-month-old patient with a large cardiac tumor. The transplant was successful, and the recipient had a good organ function at a follow-up of 7.2 years.

3.3 | Refusals

For all the 136 hearts offered, 284 reasons for refusal were given by the transplantation centers and noted in SOAS (Figure 2).

A virtual simulation of the allocation process was performed retrospectively for all organs offered that were not accepted in Switzerland ($n=110$; see Figure 3). For these hearts, a cumulative total of 244 matches were found with potential recipients on the waitlist at the same time. The decision-making process was carried out twice for all potential donor–recipient matches. Hearts that were refused for reasons other than non compatible recipient or LVEF were excluded from this simulation ($n=25$; Figure 3). After using the traditional criteria, three matches remained. However, the application of the extended criteria opened the potential for successful heart transplantation for 20 more recipients.

Of the 26 transplanted hearts, five were accepted and transplanted by one center after having been refused by other centers for reasons other than noncompatible recipient (Table 3).

4 | DISCUSSION

This study analyzed the allocation process of pediatric heart transplantation in Switzerland. The rate of accepted donor heart offers was 19%. This is even lower than a former Swiss cohort, which found an overall acceptance rate of 27.5% of pediatric and adult hearts between 2007 and 2013 in Switzerland.¹ Data from Eurotransplant and the US showed a higher acceptance rate of 54.8%¹⁴ and 66%³ respectively for pediatric donors. This low acceptance rate in Switzerland may be explained in part by the relatively small population in Switzerland: For example, the probability of finding a perfect match between a donor and a recipient currently on the waitlist within the Swiss population of 8.7 million inhabitants is lower than within the area of Eurotransplant, which comprises a population of approximately 137.5 million people. In our cohort, of the 16 children and two adults receiving transplants, 13 (72%) received an organ from a donor outside Switzerland. Smooth international cooperation including a platform facilitating exchange of organs donated in EU member states (FOEDUS) is an essential prerequisite for the Swiss heart transplant program.¹⁵

The acceptance rate can vary from 10 to 60% between centers.¹⁶ The ultimate goal remains a low waitlist mortality and optimal post-transplant outcome.¹⁶ Consequently, it is important to question the

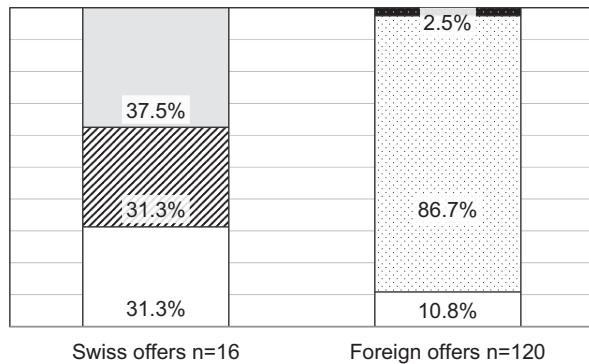
TABLE 1 Donor characteristics of the total cohort and comparison between accepted (decision yes) and refused (decision no) hearts.

	Total organ offers	Decision Yes	Decision No	p-value Yes versus no
Number of organ offers (n)	136	26	110	
Age (years); median (range)	3.4 (0–15.9)	5.5 (0.2–14.9)	3.0 (0–15.9)	.05
Sex, female n (%)	59 (43)	10 (38)	49 (44)	.7
Swiss offers n (%)	16 (12)	10 (38)	6 (5)	<.001
Blood group (n)				
A	67	14	53	.3
B	27	3	24	
AB	16	0	16	
O	26	9	17	
Cause of death (n)				
Anoxia	56	10	46	.6
Cerebral trauma	47	39	38	
Cerebral hemorrhage	10	3	7	
Cerebral disease	6	0	6	
Other	15	4	11	
Missing	2	0	2	
Ventricular function (LVEF; n)				
<40%	7	0	7	.2
40–50%	5	2	3	
>50%	92	20	72	
Missing	32	4	28	
Glomerular filtration rate (n)				
eGFR <30	2	0	2	1.0
eGFR ≥30	112	25	87	
Missing	22	1	21	
Cardiopulmonary resuscitation (n)				
No CPR	71	14	57	.9
≤20min	25	4	21	
>20min	33	7	26	
Missing	7	1	6	
Inotropic use (n)				
Yes	103	20	83	1.0
No	30	5	25	
Missing	3	1	2	
Infection (n)				
Yes	38	5	33	.2
No	85	21	64	
Missing	13	0	13	
EBV IgG (n)				
Positive	55	16	39	.8
Negative	20	7	23	
Missing	51	3	48	

TABLE 1 (Continued)

	Total organ offers	Decision Yes	Decision No	p-value Yes versus no
CMV IgG (n)				
Positive	53	14	39	.3
Negative	56	11	55	
Missing	17	1	16	

Note: Inotropic use: Inotropic use after admission (dobutamine, dopamine, norepinephrine, or adrenaline), Infection: Infection with use of antibiotics. Abbreviations: CMV, cytomegalovirus; CPR, cardiopulmonary resuscitation; EBV, Epstein–Barr virus; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); HBV, hepatitis B virus anti-HBc/HBs Ag; HCV, hepatitis C virus Ab; HIV, human immunodeficiency viruses; LVEF, left ventricular ejection fraction.



- Accepted in Switzerland, transplanted outside Switzerland †
- Discarded
- ▨ Not accepted in Switzerland, further transplant status not known ‡
- ▩ Not accepted in Switzerland, transplanted outside Switzerland
- Transplanted in Switzerland

FIGURE 1 All 136 pediatric heart offers sorted by Swiss and foreign offers. Place of transplantation is shown in different patterns indicating whether the offer was transplanted in Switzerland, outside of Switzerland or was discarded. †Foreign organs are offered simultaneously in several countries. This leads to foreign offers being offered and accepted in Switzerland, but ultimately a foreign center still receives and transplants the organ first. ‡Swisstransplant no longer monitors a foreign offer if the organ was not accepted in Switzerland; therefore, it is unknown whether the organ was finally accepted and transplanted in another country.

criteria for refusing donor organs. In this study, we identified five organs that were refused by at least one center before being accepted and successfully transplanted at another center. We think these five cases illustrate the complexity of the decision process and the challenge of objectively evaluating the medical quality of an organ that is offered.

Decisions often result from time pressure in demanding clinical situations, at times with incomplete information. A recently published international survey of 130 pediatric heart transplant centers found substantial variability in acceptance practices between centers. This is predominantly caused by two factors.¹⁷ First, the severity of a recipient's disease state, for example often encourages a center to be more generous in accepting organs offered to

TABLE 2 Recipient characteristics of all Swiss organ recipients (n = 18).

Age (years)	4.9 (0.0–50.7)
Sex, female n	11
Weight (kg)	15.0 (3.3–96)
Blood type (n)	
A	8
B	1
AB	2
O	7
Diagnosis (n)	
Congenital heart disease	7
Dilated cardiomyopathy	6
Hypertrophic cardiomyopathy	1
Restrictive cardiomyopathy	1
Other ^a	3
Mechanical circulatory support before transplantation n ^b	6
Negative virtual cross-match n ^b	14
Waitlist time (days)	135 (5–902)
Donor–recipient weight ratio	1.11 (0.6–3.42)
Ischemic time (hours:minutes)	3:45 (2:00–6:06)

Note: Data are given in median, (range).

^aOther: anthracycline-induced cardiomyopathy, ischemic heart disease, valvular cardiomyopathy, fibroma left ventricular wall.

^bMissing data in one, and two patients respectively.

a patient on ECMO than to a stable outpatient. Second, transplant program factors, such as a recent death in the same hospital, as well as concerns about programmatic restrictions from regulatory bodies. That study's authors concluded that a consensus document with a statement on the wide range of acceptance criteria may help to increase the donor pool and decrease waitlist mortality.¹⁷ Our virtual retrospective decision simulation with the rigorous application of the allocation criteria alone, found three additional compatible donor–recipient pairs in our cohort with the conventional criteria alone and 23 with the extended criteria (Figure 3). Consequently, the acceptance rate could theoretically be increased from the observed 19% to 21% or even 36%. However,

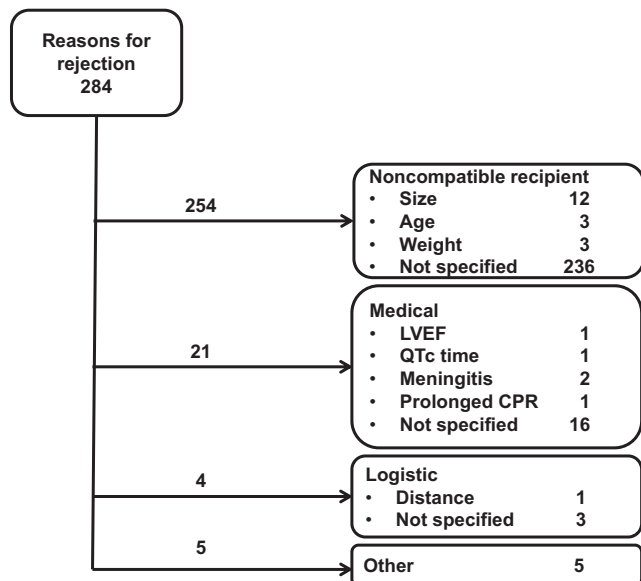


FIGURE 2 Reasons for refusal of 136 heart offers from pediatric donors in Switzerland irrespective of whether the organ has been transplanted or not. Offers are made to the three pediatric transplantation centers in Switzerland according to the ranking position of the potential recipient in the Swiss organ allocation system (SOAS) of transplantation center in charge. If a center refuses an offer, the reason for refusal is entered in SOAS. The main reason for refusal of each offer from the transplantation center was noted. Reasons are sorted by categories and additional Information when given. LVEF: left ventricular ejection fraction. CPR: Cardiopulmonary resuscitation. Other: Due to recipient (1), unstable donor (1), immunological reasons (1), refused transplantation from the donor family or judge (1), unknown reason (1). Numbers correspond to number of hearts offered.

this assumption does not include HLA matching. Especially in recipients with previous blood transfusions, increased HLA incompatibility might be expected.¹⁸

Due to growth during childhood, the issue of donor-recipient size match is very important in pediatric heart transplantation. In the Swiss allocation process, the sizes of the hearts of donor and recipient are estimated by body weight and evaluated with the donor-recipient weight ratio. The ISHLT recommends matching sizes between ratios of 0.6 and 3.0.¹² In our cohort, one patient with a donor-recipient weight ratio of 3.42 received a transplant at the age of 1 month and experienced good long-term outcome. This option is particularly useful for a recipient whose own heart has already occupied substantial space in the mediastinum, for example as a result of dilated cardiomyopathy.

As mentioned above, five donor hearts were refused at least once but successfully transplanted by another center. Reasons for the initial refusal of hearts that were later successfully transplanted (see Table 3) were (1) impaired ventricular function, (2) prolonged resuscitation time, (3) meningitis, and (4) prolonged QT duration.

(1) To assess the quality of the donor organ, the contractility of the myocardium in echocardiography is the most important factor.

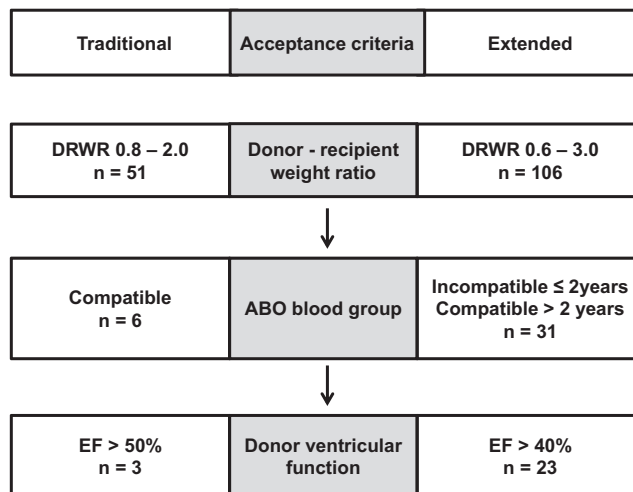


FIGURE 3 Simulation of donor and recipient matching using donor-recipient weight, blood group and donor left ventricular ejection fraction (EF). Left side: traditional criteria, right side: extended criteria. Totally 110 hearts were not accepted. There were a total of 244 donor-recipient pairs from recipients younger than 16 years. Using the traditional criteria, 3 matches remain; using the extended criteria, 23 matches remain. For this simulation, all donor-recipient pairs with other reasons for refusal than incompatible recipient or LVEF ($n=25$) were excluded.

However, echocardiography is only a momentary recording,¹⁹ and an experienced examiner is essential.¹² Refusal of an organ because of dyskinesia of the ventricular septum with otherwise good ventricular function is not justified.¹²

(2) In our cohort, five patients received hearts with donor resuscitation time between 20 and 60 min, and two hearts were even transplanted with donor resuscitation times of over 60 min. This supports the current recommendation that whether a donor has been resuscitated, and if so, for how long, are not useful criteria for refusing an otherwise suitable donor organ, especially in pediatric donors.^{8,12,20}

(3) Although few donor infections are considered as absolute contraindications,^{12,21} donor meningitis seems to remain a challenge. In this cohort, it led to two refusals. We think one of the reasons for this is the lack of solid evidence about this situation, and existing recommendations leave a lot of room for interpretation.¹² In unclear cases of donors with meningitis, an individual risk assessment involving a dedicated infectiologist should be considered.

(4) Prolonged QT duration is a common finding in ECGs of patients evaluated as donors for heart transplantation. In a sample of 257 adult donors, 32 patients (12%) had a QTc duration greater than 500 ms.²² Causes of a prolonged QT interval include brain injury, electrolyte disturbances, drug side effects, and congenital long QT syndrome.^{22,23} Sudden cardiac death in congenital long QT syndrome cannot always be excluded as a cause of donor death at the time of allocation, and some organ recipients have been described who develop ventricular tachycardia after transplantation because

TABLE 3 Patients after successful transplantation of an initially refused organ (n = 5).

Donor age (years)	Donor cause of death	Donor cardiac function	Donor country	Reason for refusal	Recipient age (years)	Recipient reason for transplantation	Recipient country	D:R weight ratio	Outcome	Follow-up (years)
0.9	Meningitis due to pneumococci	LVEF 60%	FR	Meningitis	1.2	Valvular cardiopathy	CH	0.85	Good organ function	6.2
3	Cerebral hemorrhage	Poor septum contraction, mildly reduced overall LV function	GE	Impaired left ventricular function	1.3	Congenital heart disease	CH	1.79	Good organ function	3.8
8	Anoxia	LVEF 55%	CH	Prolonged resuscitation; 60 min	5	Unknown	GE	Unknown	Unknown	Unknown
11	Meningitis	LVEF 55%	FR	Meningitis, 48h of antibiotic treatment, culture negative so far	23	Hypertrophic cardiomyopathy	CH	0.89	Good organ function	5.5
14	Anoxia	LVEF 70%	CH	Prolonged QTc-time	13	Dilated cardiomyopathy	CH	1.0	Good organ function	2.5

Note: Donor and recipient characteristics.

Abbreviations: CH, Switzerland; FR, France; GE, Germany; LV, left ventricle; LVEF, left ventricular ejection fraction.

a heart was implanted from a donor with previously unknown long QT syndrome.²² Prolonged QT duration in the donor heart is not generally considered a reason to refuse an otherwise suitable donor organ.^{12,22}

The allocation process in children cannot be analyzed independently of the allocation process in adults due to direct competition for donor organs, especially in teenagers. A recent large registry study from the US showed that 22% of pediatric donor organs were eventually allocated to adult recipients.³ Clear guidelines and objective decision criteria are required. Waitlist mortality in Switzerland is higher in children and adolescents than in young adults (17.4% vs. 11.1%).¹ Organs from adolescent donors should therefore be allocated to adolescents and larger children using the expanded weight criteria with high priority to reduce pediatric waitlist mortality.

4.1 | Limitations

This study is limited by the small number of organs included and the fact that it is a retrospective study. Furthermore, the data originated from diverse organ procurement organizations that use different forms for transmitting the information. These are not standardized and hence led to missing data. We did not include organs offered from donors over 16 years, which are also a potential group for older recipients in the pediatric group, because this study is focused on the allocation process of pediatric heart offers. Further, we did not include potential recipients over the age of 16 years. Reasons for the refusal of Swiss organs in foreign countries were not included in this study. It is not known whether organs from outside Switzerland were transplanted in other countries after they were refused in Switzerland. Some of the refused foreign offers may still have been transplanted outside Switzerland without our knowledge. Therefore, the calculated overall acceptance rate of 19% may be underestimated.

5 | CONCLUSION

This study showed a high rate of refusal of donor hearts, mostly due to the lack of compatible recipients. Other reasons, such as medical and logistical problems, accounted for only a small proportion of refusals.

The large proportion of foreign donor hearts used for Swiss recipients shows that the Swiss pediatric heart transplant program benefits greatly from good cooperation with foreign procurement organizations.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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