Heart Transplant

Effective: May 1, 2025

Next Review: March 2026
Last Review: March 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A heart transplant consists of replacing a diseased heart with a donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

MEDICAL POLICY CRITERIA

I. Human heart transplantation may be considered **medically necessary** for adults (18 years or older) with end-stage heart failure (see Policy Guidelines) when one or more of the following Criteria is met:

   A. Hemodynamic compromise due to heart failure demonstrated by any one of the following (1. – 5.) accepted indications[1]:

   1. Maximal VO2 (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism; or

   2. Refractory cardiogenic shock; or

   3. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion; or

   4. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or

5. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities; or

B. Hemodynamic compromise due to heart failure demonstrated by one of the following (1. or 2.):

   1. Any one of the following (i. – iii.) probable indications of hemodynamic compromise[1]:

      i. Maximal VO2 <14 mL/kg/min and major limitation of the patient's activities, or

      ii. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or

      iii. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction.

   2. Patient is on a ventricular assist device (VAD) or artificial heart as a bridge to transplant.

II. Human heart transplantation may be considered **medically necessary** in pediatric patients (see Policy Guidelines) when one of the following Criteria is met:

A. There is a diagnosis of heart failure with persistent symptoms at rest and any one or more of the following Criteria are met:

   1. Continuous infusion of intravenous inotropic agents; or

   2. Mechanical ventilatory support; or

   3. Mechanical circulatory support; or

B. There is a diagnosis of pediatric heart disease with symptoms of heart failure in patients who do not meet Criteria II.A but any one of the following Criteria (1 – 7) is met:

   1. Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or

   2. Cardiomyopathies or previously repaired or palliated congenital heart disease, and significant growth failure attributable to the heart disease; or

   3. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or

   4. Restrictive cardiomyopathy with reactive pulmonary hypertension; or

   5. Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or

   6. Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or

   7. Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

III.   Human heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in patients who meet criteria for heart transplantation.

IV.   Human heart transplantation or retransplantation is considered **not medically necessary** when Criterion I., II., or III. is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Adults with histories of congenital heart disease may be considered under applicable criteria for either Adult Patients (Criteria I) or Pediatric Patients (Criteria II).

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Laboratory Tests for Organ Transplant Rejection, Laboratory, Policy No. 51
2. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
3. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

SOLID ORGAN TRANSPLANTATION

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[2] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life, particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS).

HEART TRANSPLANT

In 2023, 46,632 transplants were performed in the United States procured from almost 39,679deceased donors and 6,953 living donors. Heart transplants were the third most common procedure with 4,039 transplants performed from both deceased donors in 2023. As of June 2024, there were 3,440 patients on the waiting list for a heart transplant.[3]

The majority of heart transplant recipients are now hospitalized Status 1 patients at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Patients initially listed as a Status 2 candidates may deteriorate to a Status 1 candidate before a donor organ becomes available. At the same time, as medical and device therapy for advanced heart failure has improved, some patients on the transplant list will recover enough function to become delisted.

Bakhtiyar (2020) published the results of a retrospective cross-sectional analysis of outcomes in 98,323 candidates wait-listed for heart transplantation between January 1, 1987, and December 29, 2017 in the UNOS database.[4] Overall, the one-year survival on the waiting list increased from 34.1% in 1987-1990 to 67.8% in 2011-2017 (difference in proportions, 0.34%; 95% CI, 0.32%-0.36%; p<0.001). The one-year waiting list survival for candidates with ventricular assist devices (VADs) increased from 10.2% in 1996-2000 to 70.0% in 2011-2017 (difference in proportions, 0.60%; 95% CI, 0.58%-0.62%; p< 0.001) and from 53.9% in 1996-2000 to 66.5% in 2011-2017 (difference in proportions, 0.13%; 95% CI, 0.12%-0.14%; p<0.001) for patients without VADs. Improvement in the latter was attributed to changing mechanical circulatory support indications. In sum, temporally associated increases in heart transplant waiting list survival were found for all patient groups (with or without VADs, UNOS status 1 and status 2 candidates, and candidates with poor functional status).

Magnetta (2019) reported outcomes for children on the heart transplant waiting list, comparing the periods of December 16, 2011 to March 21, 2016 (era 1), and March 22, 2016 to June 30, 2018 (era 2).[5] There was a significant decrease from era 1 to era 2 in the proportion of patients listed as status 1 (70% vs 56%; p<0.001), while the proportion of patients with congenital heart disease (CHD) significantly increased across eras (49% to 54%; p=0.018). The median time on the waitlist increased from 68 days to 78 days (p=0.005). There were no significant differences across eras in the cumulative incidence of death on the waitlist among all candidates (subdistribution hazard ratio, 0.96; 95% CI, 0.80 to 1.14; p=0.63) and among those listed status 1A (subdistribution hazard ratio, 1.16; 95% CI, 0.95 to 1.41; p= 0.14). Graft survival at 90 days was also similar across eras in the overall population and in those with CHD (p>0.53 for both).

Alshawabkeh (2018) reported on the one-year probability of the combined outcome of death or delisting due to clinical worsening for patients on the heart transplant waiting list, comparing the periods of April 1, 1986 to January 19, 1999, (early era) and January 20, 1999 to June 2, 2014 (current era).[6] For adults without CHD, the probability of the combined outcome was lower in the current era compared with the early era, regardless of whether the patient was listed in status I (14.5% vs 22.7%; p<0.0001) or 2 (9.0% vs 12.8%, p<0.0001). When comparing the current and early eras in adults with CHD, a reduction in the probability of the combined outcome was demonstrated in those listed in status I (17.6% vs 43.3%, respectively; p<0.0001), whereas the outcome remained unchanged for those listed in status 2 (10.6% vs 10.4%, respectively; p=0.94).

In adults with CHD, factors associated with waitlist death or delisting due to clinical worsening within one year were also examined by Alshawabkeh (2016).[7] A multivariate analysis identified that an estimated glomerular filtration rate less than 60 ml/min/1.73 m2 (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.0 to 1.9; p=0.043), albumin less than 3.2 g/dl (HR, 2.0; 95% CI, 1.3 to 2.9; p<0.001), and hospitalization at the time of listing in the intensive care unit (HR, 2.3; 95% CI, 1.6 to 3.5; p<0.001) or a non-intensive care hospital unit (HR, 1.9; 95%

CI, 1.2 to 3.0; p=0.006) were associated with waitlist death or delisting due to clinical worsening within one year.

Johnson (2010) reported on waiting list trends in the U.S. between 1999 and 2008.[8] An increasing trend of adult patients with congenital heart disease and retransplantation was noted. The proportion of patients listed as Status 1 continued to increase, even as waiting list and post-transplant mortality for this group decreased. Meanwhile, Status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years. This is an update to what Lietz and Miller published in 2007, where they reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005.[9] One year survival for UNOS Status 1 candidates improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared to 81.8% in the earlier time period.

As a consequence of improved survival in those on transplant waiting lists, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (VO2), which is measured during maximal exercise, is one measure that has been suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology (ACC) has adopted maximal VO2 as one criterion for patient selection.[1] Studies have suggested that transplantation can be safely deferred in those patients with a maximal VO2 of greater than 14 mL/kg/min. The importance of maximal VO2 has also been emphasized by an American Heart Association Scientific Statement addressing heart transplant candidacy.[10] In past years, a left ventricular ejection fraction (LVEF) of less than 20% or a New York Heart Association (NYHA) Class III or IV status may have been used to determine transplant candidacy. However, as indicated by the ACC criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than maximal VO2 have been proposed as predictive models in adults.[11-14] The Heart Failure Survival Scale (HFSS) and Seattle Heart Failure Model (SHFM) are two examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information regarding pharmacologic and device usage is incorporated into the model, permitting some estimation of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy and colleagues[15] introduced the model using multivariate analysis of data from the PRAISE1 heart failure trial (n=1,125). Applied to the data of five other heart failure trials, the SHFM correlated well with actual survival (r: 0.98, standard error of the estimate=±3). The SHFM has been validated in both ambulatory and hospitalized heart failure populations[16-18] but with a noted underestimation of mortality risk, particularly in Black adults and device recipients.[19, 20] None of these models have been universally adopted by transplant centers.

INITIAL HEART TRANSPLANT

In the U.S., over 6 million people 20 years of age and older have heart failure and 1 in 8 deaths have heart failure mentioned on the death certificate.[21, 22] The reduction of cardiac

output is considered to be severe when systemic circulation cannot meet requirements under minimal exertion.

Heart failure may be due to a number of etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart disease (CHD). The leading indication for a heart transplant has shifted over time from ischemic to nonischemic cardiomyopathy. From 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18 to 39 years (64%) and 40 to 59 years (51%) undergoing transplant operations.[23] Ischemic cardiomyopathy was the dominant underlying primary diagnosis among heart transplant recipients 60 to 69 years (50%) and 70 years and older (55%). Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of heart transplants during this time period were in adults with CHD.

HEART RETRANSPLANTATION

From 2008 to 2015, approximately 4% of heart transplants were repeated transplantations.[3] As of June 2020, there were 106 patients on the waitlist for a repeat heart transplant. Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The United Network for Organ Sharing does not have separate organ allocation criteria for repeat heart transplant recipients.

REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse

events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. Due to the nature of the population discussed herein, there are no RCTs comparing heart transplantation with alternatives, including left ventricular assist devices (LVADs). Systematic reviews are based on case series and registry data. RCTs published on related topics (e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy) are not relevant to this evidence review.

INITIAL HEART TRANSPLANT

Survival after heart transplant

According to the Organ Procurement and Transplantation Network (OPTN), Kaplan-Meier survival rates for heart transplants performed during 2008-2015 based on available U.S. data as of June 14, 2024, the one-year survival after heart transplant was 90.3% (95% confidence interval [CI], 89. 6% to 90.9%) and 90.7% (95% CI, 89.6% to 91.7% for men and women, respectively.[3] Three-year survival rates were 84.7% (95% CI, 83.8% to 85.5%) and 84.1% (95% CI, 82.7% to 85.4%) for men and women, respectively, and five-year survival rates were 77.8% (95% CI, 76.8% to 78.8%) and 75.9% (95% CI, 74.2% to 77.6%), respectively.

A systematic review by Almarsi (2019) was conducted to identify new variables associated with transplant outcomes that are not currently collected by the Organ Procurement and Transplantation Network (OPTN).[24] Eighty-one unique studies including 1,193, 410 transplant patients with median follow-up of 36 months posttransplant were included. Among the 108 unique risk factors identified, 104 were recipient-related and 4 were donor-related. The strongest relative association measure for a heart transplant outcome with a risk factor was 8.6 (recipient with the previous Fontan operation).

A retrospective case-control study by Suarez-Pierre (2021) was published that compared survival after heart transplantation with that of the general population.[25] Data from 31,883 adults in the OPTN who had undergone heart transplantation between 1990 and 2007 were matched (5:1) to control subjects (n=159,415) based on age, sex, race, and state of permanent residency. The ten-year survival of heart transplant recipients was 53%. The population expected mortality rate was 15.9 deaths per 100 person-years with an observed rate of 45.1 deaths per 100 person-years (standardized mortality rate [SMR] 2.84; 95% confidence interval, 2.82 to 2.87). Over time, the standardized mortality ratios declined (1990 to 1995, 3.09; 1996 to 2000, 2.90; 2001 to 2007, 2.58) and the largest discrepancies between observed and expected survival were in female (SMR 3.63), black (SMR 3.67), and Hispanic (SMR 4.12) transplant recipients.

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Nguyen (2017) investigated the benefit of heart transplantation compared with waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in the OPTN between July 2006 and December 2015.[26] Net benefit

from heart transplantation was evident across all estimates of donor-recipient status 1A and 1B candidates: status 1A (lowest-risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR=0.52; 95% CI, 0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR=0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR=0.66; 95% CI, 0.58 to 0.74). Status 2 candidates showed a benefit from heart transplantation; however, survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Lund (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation during 2000-2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.[23] Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR=1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR=1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR=1.16; 95% CI: 1.10 to 1.23; n=7822), congenital (HR=1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR=1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs non-ischemic cardiomyopathy), and retransplant (HR=1.18; 95% CI, 1.02 to 1.35; n=489) were associated with post-transplant mortality risk at 10 years.

Ting (2016) published a report that retrospectively evaluated outcomes of 134 patients one month to 78 years old (average 28) who received mechanical circulatory support for acute myocarditis with cardiogenic shock, between 1994 and 2014.[27] Patients recovering without a transplant were compared to those who received a transplant under mechanical circulatory support. 54% of patients survived on mechanical circulatory support, without transplant. Only 5% of the patients underwent transplant. The authors concluded transplant survival under mechanical circulatory support had favorable mid- and long-term outcomes.

Starling (2016) and Svobodova (2016) published studies evaluating transplant outcomes based on biomarkers and/or antibodies. Sterling published a one year observational, multicenter, cohort study in which 200 heart transplant patients were evaluated for biomarkers that could predict heart transplant outcomes.[28] Laboratory tests included anti-AHL antibody analysis, ELISPOT Panel of reactive T cell (PRT) assays, plasma angiogenesis-related proteins, peripheral blood and tissue gene expression profiling. Svobodova published a single-center retrospective study that evaluated antibody-mediated rejection (AMR).[29] Data was analyzed for pre- and post-transplant antibodies and antigens in transplant recipients and/or donors. Median follow-up was 39 months. Starling concluded it is still difficult to find reliable biomarkers that can determine heart transplant outcomes. Svobodova stated monitoring pre- and post-transplant antigens and antibodies may predict rejection.

Rana (2015) conducted a retrospective analysis of solid organ transplant recipients registered in the UNOS database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.[30] Transplant recipients were compared with patients listed for transplant, but who did not receive a transplant after propensity score matching based on a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

A 2013 study examined characteristics of patients who survived longer than 20 years after heart transplantation at a single center.[31] Thirty-nine heart transplant recipients who survived over 20 years post-transplant were compared to 98 patients who died between one and 20-years post-transplant. Independent factors associated with long-term survival were younger

recipient age i.e., <45 years versus 45 years and older (OR: 3.9, 95% CI: 1.6-9.7) and idiopathic cardiomyopathy i.e. versus other etiologies (OR: 3.3, 95% CI: 1.4-7.8).

Bhama (2013) published results from study that reported on survival outcomes for heart transplantation in a cohort of adults with congenital heart disease (CHD) and identified risk factors for mortality that would help guide recipient and donor selection.[32] A retrospective analysis identified 19 patients that had transplantation for CHD and compared to 428 transplant patients that underwent transplantation for conditions other than CHD. There was no significant difference in survival (CHD vs control) at 30 days (89% vs 92%, p = 0.5567), one year (84% vs 86%, p = 0.6976), or five years (70% vs 72%, p = 0.8478). The only significant predictor of death in the CHD group was donor organ ischemic time >four hours (HR 13.26, 95% CI 1.3 to 132.2, p = 0.028). Authors suggested that adults with CHD have excellent early and mid-term survival after heart transplantation.

A 2012 study by Kalic analyzed prospectively collected data from the United Network for Organ Sharing (UNOS) registry.[33] The analysis included 9,404 individuals who had survived 10 years after heart transplant and 10,373 individuals who had died before 10 years. Among individuals who had died, mean survival was 3.7 years post-transplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included:

- Age younger than 55 years (odds ratio [OR]: 1.24, 95% confidence interval [CI]: 1.10 to 1.38),
- Younger donor age (OR: 1.01, 95% CI: 1.01 to 1.02),
- Shorter ischemic time (OR: 1.11, 95% CI: 1.05 to 1.18),
- White race (OR: 1.35, 95% CI: 1.17 to 1.56), and
- Annual center volume of nine or more heart transplants (OR: 1.31, 95% CI: 1.17 to 1.47).

Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included:

- Mechanical ventilation (OR: 0.53, 95% CI: 0.36 to 0.78), and
- Diabetes (OR: 0.67, 95% CI: 0.57 to 0.78).

Jalowiec (2011) compared clinical outcomes in sex-matched and sex-mismatched heart transplant recipients.[34] They retrospectively reviewed data from 347 heart transplant recipients; 237 (78.7%) received a heart from a same-sex donor, 40 (11.5%) cases involved a female donor and male recipient, and 34 (9.8%) cases involved a male donor and female recipient. There was not a statistically significant difference in the mortality rate during the first month post-transplant between the sex-matched and either sex-mismatched group. In adjusted analyses, two of the other nine study outcomes differed significantly among the three groups. The male donor-female recipient group had significantly more treated rejection episodes during the first year post-transplant and significantly more days of rehospitalization after the initial discharge than either of the other two groups. The incidence of steroid-induced diabetes, cardiac allograft vasculopathy, non-skin cancers, number of intravenous (IV)-treated infections post-transplant, and initial hospital length of stay were not significantly different among groups.

Pediatric considerations

The highest one- and three- year survival rate among pediatric patients undergoing heart transplant in the US, during 2008-2015, were 11-17 year old patients according to the Organ Procurement and Transplantation Network (OPTN).[3] Patients younger than one-year-old had the lowest one-, three-, and five-year survival among pediatric patients.

Khan (2021) published the results of a retrospective analysis of heart transplant survival in children with congenital heart disease with or without heterotaxy syndrome.[35] Waitlist outcomes and survival post-listing and transplant were analyzed from 4814 children of whom 196 (4%) had heterotaxy. No differences in waitlist outcomes of transplant, death, or removal were found between patients with or without heterotaxy. Post-transplant survival was worse for children with heterotaxy: one-year survival 77.2% vs. 85.1%, with and without heterotaxy, respectively. In addition, heterotaxy was an independent predictor for early mortality in the earliest era (1993-2004), HR 2.09, CI 1.16-3.75, p = 0.014, however, this improved over time. Lower freedom from infection and from severe rejection was found in patients with heterotaxy, but no difference in vasculopathy or malignancy was identified.

Rossano (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry. Among 12,091 pediatric patients undergoing heart transplantation during 1982-2014, the overall median survival was 20.7 years for infants, 18.2 years for children ages 1 to 5 years, 14.0 years for those ages 6 to 10 years, and 12.7 years for those ages 11 to 17 years. As the first year posttransplant represents the greatest risk for mortality, survival conditional on survival to one year was longer.[36]

Kulkami (2016) published an evaluation of a multicenter prospective single ventricle reconstruction trial to determine outcomes of infant patients with a single ventricle who were listed for transplant after the Norwood procedure.[37] A public database was used to compare infants while on the waiting list and after transplant. Risk factors were also evaluated for those patients put on the waiting list for a transplant and for those who survived without a transplant. Of 555 patients 33 were listed and underwent transplant. One-year survival after being put on the waiting list, including those that died after transplant was 48%. Diagnosis for being put on the transplant list after the Norwood procedure, included worsening right ventricular function, non-hypoplastic left heart syndrome, and a complex intensive care unit stay. The authors determined patients having heart transplant as a rescue procedure within a year of the Norwood procedure had a higher risk of complications and mortality.

Garbern (2016) published a study that evaluated transplant outcomes for pediatric patients with myocarditis versus dilated cardiomyopathy (DCM).[38] During the study 137 children with myocarditis and 1,249 children with DCM underwent heart transplant. Data was taken from the Organ Procurement and Transplant Network (OPTN) database. The data for children with myocarditis was evaluated for a higher risk of mortality pre-transplant. The authors noted several study limitations including that they could not confirm data accuracy, but stated after the adjustment for severity of illness, children with myocarditis were not at a higher risk of mortality pre- and post-transplant than patients with DCM.

According to OPTN data, in 2015, 423 heart transplants were performed in children younger than 18 years of age.[3] Five-year survival rates by age group were: less than one year: 68.6% (95% CI, 62.0% to 75.1%); one to five years: 69.4% (95% CI, 64.1% to 74.7%); six to ten years: 73.1% (95% CI, 66.7% to 79.5%); and 11-17 years: 75.1% (95% CI, 72.6% to 77.5%).

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia in 2014.[39] From 1987 to 2011, 99 adolescents (age, 13-18) heart transplants were

performed with myocarditis and 456 adolescents with coronary heart disease (CHD). Among adolescent transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly less than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

According to the International Society for Heart and Lung Transplantation, 532 heart transplants in children younger than 18 years-old were reported worldwide in 2010.[40] This number compares to 543 reported in 2009. Among the pediatric transplants, about 25% were in infants younger than age one year, 37% were in children between the ages of one and 10 years, and 38% were in adolescents between the ages of 11 to 17 years. In infants, the most common indications for heart transplant were congenital heart disease (56%) and cardiomyopathy (40%). For children older than 10 years of age, the most common indication was cardiomyopathy (63%). Median survival has varied with age of the transplant recipient. Median survival was 19.2 years for infants, 15.6 years for one to 10 year-olds, and 11.9 years for 11-17 year-olds.

In 2011, a retrospective review of pediatric cardiac transplantation patients was published by Auerbach.[41] A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at one year and 68% at five years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was 82% at one year and 72% at five years. In multivariate analysis, the authors found that congenital heart disease (HR: 1.6, 95% CI: 1.02-2.64) and requiring mechanical ventilation at the time of transplantation (HR: 1.6, 95% CI: 1.13-3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only one center.

Patel (2010) presented a retrospective review of echocardiography and serum markers as a predictor of death or need for transplantation in newborns, children, and young adults with heart failure.[42] A total of 99 children with 139 admissions were evaluated on LVEF and tricuspid regurgitation, as well as on various serum markers for their predictive ability of death or need for transplantation in a stepwise multivariate Cox regression model. While brain natriuretic peptide (BNP) and tricuspid regurgitation were not predictive of need for transplantation, ejection fraction and lymphocytosis were predictive (ejection fraction odds ratio [OR]: 0.94, 95% CI: 0.90-0.98; for lymphocytosis, OR 5.40, 95% CI: 1.67–17.4). Serum levels of creatinine and sodium were also predictive. Clinical prediction rules based on these findings have not been compared to current strategies and await clinical validation.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.[43] Of 3,098 children (younger than 18 years of age) listed between 1999 and 2006, a total of 1,874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1,943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population

with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR]: 3.1), ventilator support (HR: 1.9), listing status 1A (HR: 2.2), congenital heart disease (HR: 2.2), dialysis support (HR: 1.9), and non-white race/ethnicity (HR: 1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

HEART RETRANSPLANTATION

Chen (2022) evaluated outcomes after heart re-transplantation in recipients > 60 years. A total of 1026 adult patients undergoing isolated heart re-transplantation were identified (> 60 years, n=177; ≤ 60 years, n=849).[44] Older recipients were more likely to be male and have diabetes or previous malignancies with higher baseline creatinine. They more frequently required pre-transplant ECMO (11.9% vs. 6.8%, p=0.02) and received re-transplantation due to primary graft failure (13.6% vs. 8.5%, p=0.03). After transplant, older recipients had a higher incidence of stroke (6.8% vs. 2.6%, p=0.01) and dialysis requirements (20.3% vs. 13.2%) before discharge (both p<0.05), and more frequently died from malignancy-related causes (16.3% vs. 3.9%, p<0.001). After adjustment, recipient age >60 was associated with an increased risk of both 5-year (HR 1.42, 95% CI 1.02-2.01, p=0.04) and 10-year mortality (HR 1.72, 95% CI 1.20-2.45, p=0.003).

Zhu (2022) evaluated outcomes after heart retransplantation for 123 patients (112 adult and 11 pediatric patients) as compared to those who received a primary heart transplant at a single-center over a 50-year period (January 6, 1968 to June 2019).[45] The indications for retransplantation included cardiac allograft vasculopathy (80%), primary graft dysfunction (15%), and refractory acute rejection (5%). The mean time interval between the primary and retransplant was 6.4 years. Patients who underwent a retransplantation were significantly more likely to have hypertension (73.3% vs. 53.3%; p=.0022), hyperlipidemia (66.7% vs. 30.7%; p<.0001), and require dialysis (11.7% vs. 2.9%; p=.0025) as compared to those undergoing a primary heart transplant. After matching, postoperative outcomes and complications including hospital stay (mean 22.9 vs. 25.8 days; p=.49), intensive care unit stay (mean 12.2 vs. 9.9 days; p=.48), respiratory failure (41.7% vs. 20.6%; p=.083), dialysis (21.2% vs. 24.2%; p=.82), pneumonia (12.9% vs. 9.6%; p=.48), septicemia (1.6% vs. 9.4%; p=.10), and rejection within the first year after transplantation requiring hospitalization (21.5% vs. 26.2%; p=.82) were similar between the retransplant and primary transplant groups, respectively. Matched median survival after retransplantation was 4.6 years versus 6.5 years after primary heart transplantation (p=.36).

In a study analyzing UNOS data from January 1996 to November 2017, Miller (2019) reported that 349 (0.6%) early/acute retransplants (occurring ≤ one year after the previous transplant) and 2,202 (3.5%) late retransplants (occurring > one year after the previous transplant) were performed from a sample of 62,112 heart transplants.[46] Compared with a matched group of patients undergoing initial transplantation, patients undergoing late retransplantation were not at an increased risk of death (HR, 1.08; p=0.084) or the combined outcome of death or retransplantation (HR, 1.07; p=0.114). Additionally, patients undergoing late retransplant had comparable rates of one-year all-cause mortality when compared to patients undergoing initial transplant (13.8% vs 14.5%, respectively; p=0.517). Conversely, patients undergoing early/acute transplant had higher rates of one-year all-cause mortality when compared to patients undergoing initial transplant (35% vs 21.6%; p<0.001). Furthermore, early/acute

retransplantation was associated with an increased risk of all-cause mortality (HR, 1.79; p<0.001) and the combined outcome of death or retransplantation (HR, 1.72; p<0.001).

An analysis of OPTN data from 1995 to 2012 by Belli (2014) reported that 987 retransplants were performed (of 28,464 heart transplants, 3.5% of all transplants).[47] Median survival among retransplant recipients was 8 years. The estimated survival at 1, 5, 10, and 15 years following retransplant was 80%, 64%, 47% and 30%, respectively. Compared with primary transplant recipients, retransplant patients had a somewhat higher risk of death (risk ratio [RR]=1.27, 95% CI, 1.13 to 1.42).

A number of studies have reviewed clinical experience with heart retransplantation in adults. In 2013, Saito published a retrospective review of data on 593 heart transplants performed at their institution; 22 of these (4%) were repeat transplantations.[48] The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in seven patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in five patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7 of 22 patients). Among patients who survived the first 30 days (n=15), 1-, 5- and 10-year survival rates were 93.3%, 79% and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82% and 63%, respectively. An interval of one year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of nine patients (33.3%) with less than a year between the primary and retransplantation survived to 30 days. In comparison 12 of 13 patents (92%) with at least one year between primary and retransplantation were alive at 30 days after surgery.

Tjang (2008) published a systematic review of this literature that identified 22 studies reporting clinical outcomes of heart retransplantation in patients over 18 years old.[49] The most common indications for retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range: 5% to 38%). Some of the factors associated with poorer outcome after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure and an initial diagnosis of ischemic cardiomyopathy.

Topkara (2005) reviewed data on 766 adult patients who underwent heart transplantation between 1992 and 2002.[50] Forty-one (5%) of patients underwent repeat transplants; the indication for retransplantation was transplant-related coronary artery disease in 37 of 41 (90%) of these patients. Due to early experience with retransplantation, criteria at this institution were changed in 1993 so that patients with intractable acute rejection within 6 months of the initial transplant were ineligible for repeat transplants. One and five-year survival rates were 85.1% and 72.9%, respectively after primary transplantation and 72.2% and 47.5%, respectively after retransplantation. Survival rates were significantly lower in the retransplantation group, p<0.001. The authors did not report survival rates stratified by the length of time between initial and repeat transplantations.

Pediatric Considerations

Vazquez (2022) published an evaluation of retransplantation patients from the Pediatric Heart Transplant Society (PHTS) database analysis of retransplantation patients <18 years of age over three decades (Era 1: 1993-2001, Era 2: 2002-2010, Era 3: 2011-2018).[51] Survival was lower (p < .0001) for retransplant (n = 222) compared to primary transplant (n = 6548) (median 9.3 vs 20.2 years). Median survival increased from Era 1 to 2 (4.8 vs 9.3 years; p < .0001) with

no incremental change in Era 3. Era 2 and 3 retransplants had a longer inter-transplant interval (p < .0001), were less frequently for early graft failure (p = .0004) or acute rejection (p = .007), more frequently from a ventricular assist device (p = .0014), and less frequently from extracorporeal membrane oxygenation (p = .0024). Predictors of graft loss included Era 1 (HR 10.55, p = .001), congenital heart disease (HR 4.42, p = .01), inter-transplant interval <1 year (HR 5.34, p = .002), and mechanical support (ventricular assist device HR 7.47, p = .0042; extracorporeal membrane oxygenation HR 10.09, p < .0001). For each 1-year increase in inter transplant interval, graft loss risk decreased by 1.15 (p = .0002). Retransplantation was associated with more rejection, infection, and allograft vasculopathy. The authors conclude that graft survival has improved in pediatric retransplant and that retransplantation should be avoided in the setting of early graft failure especially requiring mechanical support.

Azeka (2020) published a retrospective cohort study reporting on patients who underwent primary heart transplant (PTx) <18 years old and subsequent retransplant (RTx) due to coronary allograft vasculopathy (CAV). [52] The maintenance immunosuppression protocol was double immunosuppression. Between 1992 and 2018, 200 children underwent heart transplantation. Ten re-transplantations were performed, for which 7 (70%) were for CAV. Ages at RTx ranged from 11.5 to 29.3 years (19.1 ± 5.68 years; median 18.2 years). The mean time between PTx and RTx was 12.9 ± 3.4 years (median 13.4 years). The Kaplan-Meier survival rate at 1 month, 3 years, and 5 years was 85.7%, 71.5%, and 47.6%, respectively. The authors conclude that cardiac RTx can be a management option for CAV in patients who have undergone PTx in childhood with double immunosuppression therapy.

As with initial heart transplants, children waiting for heart retransplantation have high waitlist mortality. Alsoufi (2015) published results from a retrospective analysis (1988 to 2013) that examined their experience with heart transplantations in pediatric patients with underlying congenital heart disease.[53] The study included sixteen patients who underwent primary heart transplantation. Participants were predominately male, and had a median age of 3.8 years. Competing risks analysis showed that at 10 years after heart transplantation, 13% of patients had undergone retransplantation, 43% of patients had died without retransplantation, and 44% of patients were alive without retransplantation. After retransplantation, 52% of patients were alive and 18% of patients had undergone a second retransplantation. Overall 15-year survival after initial heart transplantation was 41%. It is important to note this study has methodological considerations, which include but are not limited to, a small sample size; therefore, generalizability of results is limited.

Bock (2014) evaluated data on 632 pediatric patients who were listed for a heart retransplant at least one year (median, 7.3 years) after the primary transplant.[54] Patients' median age was four years at the time of the primary transplant and 14 years when they were relisted. Median waiting time was 75.3 days and mortality was 25.2% (159 of 632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<0.01).

Copeland (2014) published results from a retrospective chart review (n=183) and evaluated late survival among pediatric heart transplant patients, living for more than 15 years after transplant.[55] A total of 32 deaths were reported due to the following conditions: cardiac allograft vasculopathy (CAV); 11 (34.3%); posttransplant lymphoproliferative disease, 18.8%; acute rejection, 12.5%; sepsis, 6.3%; multiorgan failure, 3.1%; and unknown reasons, 25%. A total of 30 patients required cardiac retransplantation due to CAV. The authors concluded that heart transplantation in pediatric patients results in acceptable long-term survival. In patients

who develop CAV and renal dysfunction, heart retransplantation is an acceptable form of palliative treatment.

Friedland-Little (2014) published results from a retrospective analysis (1985-2011) of pediatric and young adult survivors who had undergone repeat heart transplantations.[56] Patients were included in the review who had a primary heart transplant before the age of 21, and had undergone a third transplant. Patients were matched 1:3 with a control group of second heart transplant patients by age, era and re-transplant indication. The authors found no difference between third heart transplant patients (n=27) and the control second heart transplantation patients (n=79) with respect to survival (76% vs 80% at one year, 62% vs 58% at five years and 53% vs 34% at 10 years, p = 0.75). However, generalizability of the study's results may be limited due to methodological limitations, such as small sample size.

Mahle (2005) reviewed data from the United Network for Organ Sharing (UNOS) on heart retransplantation in patients less than 18 years old.[57] A total of 219 retransplantations occurring 1987 to 2004 were identified. The median age at initial transplant was 3 years old and the median age at retransplantation was nine years old. The median interval between initial procedure and retransplantation was 4.7 years. The most common indications for retransplantation were coronary allograft vasculopathy (n=111, 51%), non-specific graft failure (n=34, 18%) and acute rejection (n=19, 9%). Retransplantation was associated with worse overall survival than initial transplantation. One,five, and ten year survival rates were 83%, 70% and 58%, respectively after primary transplantation and 79%, 53% and 44%, respectively after retransplantation. The most common causes of death after retransplantation were acute rejection (14%), coronary allograft vasculopathy (14%) and infections (13%).

In both the adult and pediatric studies, poorer survival after retransplantation than initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events. The increased mortality from retransplantation appears to be mainly from increased short-term mortality. Longer-term survival rates after retransplantation seem reasonable, especially when patients with a higher risk of poor outcomes (e.g., those with a shorter interval between primary and repeat transplantation) are excluded. Also, patients with failed initial transplant have no other options besides a retransplantation.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Pretransplant malignancy is considered a relative contraindication for heart transplantation considering this has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population,

Mistiaen (2015) conducted a systematic review to study the posttransplant outcome of pretransplant malignancy patients.[58] Most selected studies were small case series. Mean patient age varied from 6 years to 52 years. Hematologic malignancy and breast cancer were the most common type of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy was mostly the common reason for transplantation in 4 case series, chemotherapy related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality varied between 0% and 33%, with small sample size potentially explaining the observed variation, One large series reported similar short-term and long-term posttransplant survival of chemotherapy related (N=232) and other nonischemic cardiomyopathy (N=8890) patients. The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients. Similar findings were observed for 1-year survival in smaller series. Two-, 5-, and 10-year survival rates among pretransplant malignancy patients were also comparable with other transplant patients. In addition to the nonmalignancy related factors such as cardiac, pulmonary, and renal dysfunction, two malignancy related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival compared with a longer interval (<60% vs >75%). Patients with prior hematologic malignancies had an increased posttransplant mortality in three small series. Recurrence of malignancy was more frequent among patients with a shorter disease-free interval, 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.

Yoosabai (2015) conducted a retrospective review among 23,171 heart transplant recipient in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of posttransplant malignancy.[59] Posttransplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with increased risk of overall posttransplant malignancy (subhazard ratio [SHR], 1.51; p<0.01), skin (SHR=1.55, p<0.01), and solid organ malignancies (SHR=1.54, p<0.01) on multivariate analysis.

ISHLT guidelines have recommended to stratify each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The guideline also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

OLDER AGE

Jamil (2017) conducted a retrospective study of age as it relates to primary graft dysfunction after heart transplantation.[60] Of the 255 heart transplants studied, 70 (27%) recipients were 65 years and older and 185 were younger; there were no significant differences in post-transplant morbidity (all p>0.12) or one-year survival between groups (p=0.88). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; p=0.037). Study limitations included the single-center design, lack of data on long-term survival, and the potential for selection bias in retrospective studies.

Cooper (2016) published a retrospective cohort study evaluating transplant outcomes in elderly patients, by using data from the United Network for Organ Sharing database. Data on

three groups of patients 18-59, 60-69 and greater than or equal to 70 years of age were compared for five-year survival rates. The authors noted that patients greater than or equal to 70 had more ischemia and renal dysfunction than the 60-69 age group and received transplants from older donors who were more ill or had a history of drug abuse. Five-year survival rates were 26.9% for the 18-59 age group, 29.3% for the 60-69 age group, and 30.8% for the greater than or equal to 70 age group. The authors also noted limitations with this retrospective review including but not limited to potential risk of bias with patient transplant selection and quality of the data. The authors concluded the greater than or equal to 70 age group showed no significant difference in outcomes from the 60-69 age group and should not be excluded from receiving a transplant.

Awad (2016) reported on a single-center retrospective review of 704 adults who underwent heart transplantation from 1988 to 2012 to investigate the mortality and morbidity rates of heart transplantations among recipients 70 years of age and older (n=45) compared with recipients younger than 70 years (n=659).[61] The older and younger groups had similar 1-year (93.0 vs 92.1; p=0.79), 5-year (84.2 vs 73.4; p=0.18), and 10-year (51.2 vs 50.2; p=0.43) survival rates, respectively.

Kilic (2012) analyzed data from the UNOS on 5,330 patients age 60 and older (mean age 63.7 years) who underwent heart transplantation between 1995 and 2004.[62] A total of 3,492 individuals (65.5%) survived to five years. In multivariate analysis, statistically significant predictors of five-year survival included younger age (OR: 0.97, 95% CI: 0.95 to 1.00), younger donor age (OR: 0.99, 95% CI: 0.99-1.00), white race (OR: 1.23, 95% CI: 1.02 to 1.49), shorter ischemic time (OR: 0.93, 95% CI: 0.87-0.99), and lower serum creatinine (OR: 0.92, 95% CI: 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly decreased the odds of surviving to five years. Patients with two or more of these factors had a 12% lower rate of five years survival than those with none of them.

Daneshvar (2011) examined data on 519 patients who underwent heart transplantation between 1988 and 2009 at a single institution, with a particular focus on survival differences by age group.[63] There were 37 patients who were at least 70 years-old (group 1), 206 patients between 60 and 69 years (group 2), and 276 patients younger than 60 years (group 3). Median survival was 10.9 years in group one, 9.1 years in group two, and 12.2 years in group three (non-significant difference among groups). The five-year survival rate was 83.2% in group one, 73.8% in group two, and 74.7% in group three.

PULMONARY HYPERTENSION

Findings of several studies published in 2012 and 2013 suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant.[64-67] For example, De Santo (2012) reported on 31 consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization.[64] After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing listing for heart transplant. Oral sildenafil treatment resumed following transplant. One patient died in the hospital. A right heart catheterization at three months post-transplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at one year in the 29 surviving patients. Similarly, in a study by Perez-Villa (2013) , 22 patients considered high-risk for heart transplant due to severe pulmonary hypertension were treated

with bosentan. After four months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of nine patients who refused participation in the study and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation and the one-year survival rate was 93%.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY,AND AMERICAN HEART ASSOCIATION

Guidelines from the American College of Cardiology Foundation and American Heart Association were updated in 2017.[68] Evaluation for heart transplantation was recommended for patients in whom heart failure is assessed as refractory based on New York Heart Association functional class III or IV (stage D) for heart failure after previous guideline-directed medical therapy, use of devices such as an implantable cardioverter defibrillator or a cardiac resynchronization therapy device, or surgical management.

American College of Cardiology Foundation and American Heart Association Heart failure guidelines from the American College of Cardiology Foundation, and the American Heart Association, and the Heart Failure Society of America were updated in 2022.[69]

Recommendations for cardiac transplantation by the joint committee were as follows:

- For selected patients with advanced HF [heart failure] despite GDMT [guideline-directed medical therapy], cardiac transplantation is indicated to improve survival and QOL [quality of life] (class of recommendation, 1; level of evidence, C-LD)
- In patients with stage D (advanced) HF despite GDMT, cardiac transplantation provides intermediate economic value (value statement: intermediate value)"

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

The "International Society for Heart and Lung Transplantation Guidelines for the Evaluation and Care of Cardiac Transplant Candidates—2024" updates and replaces the "Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006" and the "2016 International Society for Heart Lung Transplantation Listing Criteria for Heart Transplantation: A 10-year Update." The recommendations focus on an individualized approach rather than absolute thresholds contraindicating eligibility. For full details see the guidelines linked in the references.[70] The recommendations for the evaluation of heart transplant candidacy and includes:

- recommendations related to comorbidities (age, obesity, cancer, diabetes, cerebral and peripheral vascular disease, pulmonary disease, pulmonary hypertension, kidney disease, liver disease, connect tissue disorders and sarcoidosis, infections and vaccinations, frailty, surgical risk and bone disease).
- assessment recommendations of transplant eligibility in special populations (cardiac amyloidosis, restrictive and hypertrophc cardiomyopathy, congenital heart disease and pediatric patients.
- assessment for retransplantation
  - evaluation for retransplantation is reasonable with grade 3 CAV.
  - The benefit of retransplantation is not well established for:

- - - Graft failure due to active rejection
    - Advanced age
    - Need for durable mechanical circulatory support as a bridge to retransplantation
  - recommendations for psychosocial evaluation
  - emphasis on multidisciplinary team approach.

The updated guidelines also provide recommendations for the optimization of surveillance tor patients on the waitlist and mechanical support systems.

THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (non-randomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications:[71]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previous repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension,
- The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m2 and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m2 or the transpulmonary gradient to <15 mm Hg.

SUMMARY

There is enough research to show that heart transplantation can improve survival for certain pediatric and adult patients. Guidelines based on research recommend heart transplant for people with certain indications. Therefore, heart transplant may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that heart retransplantation can improve survival for certain pediatric and adult patients who have had a prior transplant. Guidelines based on research recommend heart retransplantation for people with certain indications. Therefore,

heart retransplantation may be considered medically necessary in patients who meet the policy criteria.

There is not enough research to show that heart transplantation or retransplantation improves health outcomes for all other indications. Therefore, heart transplantation or retransplantation is considered not medically necessary for indications when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	33940	Donor cardiectomy (including cold preservation)

Codes	Number	Description
	33944	Backbench standard preparation of donor cadaver heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
HCPCS	None	

Date of Origin: *March 2013*