
Medical Policy



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***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Combined Heart/Liver Transplantation

Description/Background

Heart-Liver Transplantation

Solid organ transplantation is now accepted treatment for selected patients with end-stage liver, kidney and heart disease. Orthotopic liver transplantation for one, is the definitive therapy for eligible patients with advanced liver disease, unresectable nonmetastatic hepatocellular carcinoma or certain metabolic diseases that can be cured via the transplant option. Orthotopic heart transplantation on the other hand, is the treatment of choice for patients with end-stage heart failure who remain significantly symptomatic and at high risk of death despite optimized medical management.

Heart transplant is medically necessary for persons with severe refractory heart failure that is associated with a life expectancy of six to twelve months. In some of these patients, chronic heart failure has led to or is associated with end-stage liver disease as well. These patients require combined transplantation of the heart and liver. Indications for combined heart/liver transplant include heart failure with associated cardiac cirrhosis, familial amyloidosis, familial hypercholesterolemia, hemochromatosis, homozygous B-thalassemia and is recommended for patients who would not be expected to survive sequential transplantation of the organs. Patients awaiting combined heart and liver transplant are enrolled through the United Network for Organ Procurement and Transplantation Network database.

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 (FDA).

The FDA 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.

Medical Policy Statement

The safety and effectiveness of a combined heart-liver transplant have been established. It may be considered a useful therapeutic option for carefully selected patients with end-stage heart and liver disease.

Inclusionary and Exclusionary Guidelines

Combined heart-liver transplants are established when transplantation of a single organ is precluded by severe disease in the other organ system, such that the patient's prognosis after combined transplantation is felt to be better than sequential transplantation.

Inclusions:

Indications for heart/liver transplantation include but are not limited to end stage heart and liver diseases that are not amenable to any other form of therapy such as:

- Familial Amyloidosis
- Heart Failure with associated cardiac cirrhosis
- Familial Hypercholesterolemia
- Hereditary Hemochromatosis
- Homozygous B-Thalassemia
- End-stage cardiac disease as indicated in related heart transplant policy
- End-stage liver disease as indicated in related liver transplant policy

Exclusions:

- Significant systemic or multisystemic disease (other than heart and liver failure)
- Active alcohol or other substance abuse that interferes with compliance to the strict treatment regimen needed following transplant.
- Malignancies metastasized to or extending beyond the margins of the heart and/or Liver.

Potential Contraindications for Transplant/Retransplant:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

Potential contraindications represent situations where proceeding with transplant is not advisable in the context of limited organ availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan should demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

- Known current malignancy, or history of recent malignancy
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end-stage disease not attributed to heart or kidney disease
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy as defined by the transplant program

All transplants must be prior authorized through the Human Organ Transplant Program

*Please note there is an individual heart transplant and liver transplant policy

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

33940	33944	33945	47135	47140	47141
47142	47143	47144	47145	47146	47147

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

Clinical Context and Test Purpose

The purpose of a combined heart-liver transplant for patients who have severe heart and/or liver disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a combined heart-liver transplant improve net health outcomes in individuals with hepatocellular disease?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with heart and/or liver disease.

Interventions

The therapy being considered is a combined heart-liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Comparators

The following practice is currently being used to make decisions about reducing the risk of heart and liver disease: medical management.

Outcomes

The general outcomes of interest are overall survival and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies).

Studies

Atluri et al (2014) analyzed short-term and long-term outcomes associated with combined heart-liver transplantations.¹ The authors reviewed demographic, perioperative, and short and long-term outcomes after this combined procedure. All 26 patients underwent successful dual organ transplant, without any episodes of primary graft dysfunction. Average length of intensive care unit stay was 10 ± 5 days, and average hospital stay was 25 ± 11 days. Kaplan-Meier analysis demonstrated excellent short-term survival (1 year, $87\% \pm 7\%$) and long-term survival (5 years, $83\% \pm 8\%$). Only 3 patients (11%) demonstrated any evidence of rejection long-term by myocardial biopsy, suggesting that concomitant hepatic transplantation may provide immunologic protection for the cardiac allograft.

Careddu et al (2015) reviewed long-term outcome of patients who have undergone combined orthotopic heart and liver transplantation (CHLT) at the University of Bologna, Italy.² Fifteen patients with heart and liver failure were placed on the transplant list between November 1999 and March 2012. The pretransplant cardiac diagnoses were familial amyloidosis in 14 patients and chronic heart failure due to chemotherapy with liver failure due to chronic hepatitis in one patient. CHLT was performed as a single combined procedure in 14 hemodynamically stable patients; there was no peri-operative mortality. The survival rates for the CHLT recipients were 93%, 93%, and 82% at 1 month and 1 and 5 years, respectively. Freedom from graft rejection

was 100%, 90%, and 36% at 1, 5, and 10 years, respectively, for the heart graft and 100%, 91%, and 86% for the liver graft. The livers of eight recipients were transplanted as a "domino" with mean overall 1-year survival of 93%. Simultaneous heart and liver transplantation is feasible and was achieved in this extremely sick cohort of patients. By adopting the domino technique, the authors were able to enlarge the donor cohort and include high-risk patients.

Reich et al (2015) reported on an institutional experience with heart-liver transplantation.³ There were 7 heart-liver transplants: 6 simultaneous (single donor) and 1 staged (2 donors). Median follow-up was 22.1 (IQR 13.2-48.4) months. Mean recipient age was 50.8 ± 19.5 years. Heart failure etiologies included familial amyloidosis, congenital heart disease, hypertrophic cardiomyopathy, systemic lupus erythematosus, and dilated cardiomyopathy. Preoperative left ventricular ejection fraction averaged 32.3 ± 12.9%. Five (71.4%) patients required preoperative inotropic support; 1 required mechanical circulatory support. The most common indications for liver transplant were amyloidosis and cardiac cirrhosis. Median Model for End-stage Liver Disease score was 10.0 (9.3-13.8). Six-month and 1-year actuarial survivals were 100% and 83.3%, with mean survival exceeding 4 years. No patient experienced cardiac allograft rejection, 1 experienced transient liver allograft rejection, and 1 developed progressive liver dysfunction resulting in death. Five developed postoperative infections and 3 (42.9%) required reoperation. Median ICU and hospital stays were 7.0 (7.0-11.5) and 17.0 (13.8-40.5) days. There were 4 (57.1%) readmissions. For carefully selected patients with coexisting heart and liver disease, combined heart and liver transplantation may offer acceptable patient and graft survival.

Beal et al (2016) reported on 159 combined heart-liver transplantations performed between January 1, 1988 and October 3, 2014 in the United States.⁴ A multitude of potential techniques to be used for combined heart and liver transplant including: orthotopic heart transplant (OHT) and orthotopic liver transplant (OLT) on full cardiopulmonary bypass (CPB), OHT with CPB and OLT with venovenous bypass (VVB), OHT with CPB and OLT without VVB, en-bloc technique and sequential transplantation. Outcomes of combined heart-liver transplant have been demonstrated to be comparable to outcomes of isolated heart and isolated liver transplant. The liver graft may provide some tolerance of other allografts.

Bryant et al (2018) described contemporary outcomes with CHLT in patients with congenital heart disease (CHD).⁵ A retrospective review of the outcomes of CHLT in CHD was conducted from October 1, 1987, to June 30, 2015, from the United Network of Organ Sharing (UNOS) database. Propensity score matched cohorts were formed for the assessment of posttransplant outcome: CHLT with CHD, CHLT without CHD, and isolated heart transplant for CHD (HT-CHD). Cohorts were matched based on age, body mass index, inotrope use, and ventilator support at the time of transplant. We assessed 30-day, 1-, 5-, and 10-year posttransplant survivals. There were 61,437 heart transplants during the study period, of which 190 (0.3%) were CHLT. Among CHLT, 41(22%) patients had CHD. In 26 (63%) of these, the indication for CHLT was hepatic congestion/cirrhosis of cardiac origin. In the matched cohorts, the overall survival for CHLT with CHD at 30 days, 1, 5, and 10 years was 95%, 86%, 83%, and 83%, respectively; for CHLT without CHD, it was 100%, 92%, 92%, and 63%, respectively (vs. CHLT with CHD: P = 0.49); and for HT-CHD, it was 90%, 84%, 63%, and 39% (vs. CHLT with CHD: P = 0.03), respectively. The posttransplant outcome of CHLT, with and without CHD, is comparable. However, there is a trend toward better survival for CHLT for CHD compared with isolated heart transplant for CHD.

Lebray and Varnous (2019) described various types of liver impairment in patients with end-stage heart failure who are awaiting heart transplantation.⁶ The liver impairment may be severe, characterized by a high model for end-stage liver disease (MELD) Score and/or the presence of ascites, both of which are associated with a high risk of failure after single heart transplantation. A liver function assessment is therefore necessary before registration on the heart transplant list, moreover in case of long-developing heart failure, such as with congenital heart disease or in the presence of risk factors for chronic liver disease including excessive alcohol consumption, metabolic syndrome or chronic viral hepatitis B or C. In these instances, screening for cirrhosis with liver biopsy and for hepatocellular carcinoma through imaging must be systematic and when present, the indication for combined heart-liver transplantation must be considered. Its benefits, however, in case of liver failure with a high MELD score or multi-organ failure remains to be demonstrated. An exception in which the liver shows no morphological or functional alteration is with familial amyloid neuropathy, during which moderate to severe heart failure implies surgical treatment consisting of a liver or even heart-liver transplantation. These must be done early and are mainly contraindicated according to the level of neurological damage.

Vaikunth et al (2019) performed a retrospective review of an experience with en bloc combined heart and liver transplantation in Fontan patients >10 years old.⁷ Six females and 3 males (median age 20.7, range 14.2-41.3 years) underwent en bloc combined heart and liver transplantation. Indications for heart transplant included ventricular dysfunction, atrioventricular valve regurgitation, arrhythmia, and/or lymphatic abnormalities. Indication for liver transplant included portal hypertension and cirrhosis. Median Fontan/single ventricular end-diastolic pressure was 18/12 mm Hg, respectively. Median Model for End-Stage Liver Disease excluding International Normalized Ratio score was 10 (7-26), eight patients had a varices, ascites, splenomegaly, thrombocytopenia score of ≥ 2 , and all patients had cirrhosis. Median cardiopulmonary bypass and donor ischemic times were 262 (178-307) and 287 (227-396) minutes, respectively. Median intensive care and hospital stay were 19 (5-96) and 29 (13-197) days, respectively. Survival was 100%, and rejection was 0% at 30 days and 1 year post-transplant. En bloc combined heart and liver transplantation is an acceptable treatment in the failing Fontan patient with liver cirrhosis.

Rizvi et al (2020) performed an electronic search to identify all studies on CHLT.⁸ Following application of inclusion and exclusion criteria, a total of seven studies consisting of 99 CHLT patients were included from the original 1864 articles. CHLT recipient mean age was 53.0 years (95% CI 48.0-58.0), 67.5% of which (95% CI 56.5-76.9) were male. 65.5% (95% CI 39.0-85.0) of patients developed heart failure due to amyloidosis whereas 21.6% (95% CI 12.3-35.2) developed heart failure due to congenital causes. The most common indication for liver transplant was amyloidosis [65.5% (95% CI 39.0-85.0)] followed by liver failure due to hepatitis C [13.8% (95% CI 2.1-54.4)]. The mean intensive care unit length of stay was 8 days (95% CI 5-11) with a mean length of stay of 24 days (95% CI 17-31). Cardiac allograft rejection within the first year was 24.7% (95% CI 9.5-50.7), including antibody mediated [5% (95% CI 1.7-15.2)] and T-cell mediated rejection [22.7% (95% CI 8.8-47.1)]. Overall survival was 87.5% (95% CI 78.6-93.0) at 1 year and 84.3% (95% CI 75.4-90.5) at 5 years. CHLT in select patients with coexisting end-stage heart and liver failure appears to offer high survival and low rejection rates.

Using the US transplant registry, Yamaguchi et al (2020) compared outcomes following sequential and CHLT.⁹ We conducted a retrospective cohort study. De-identified data were

obtained from the United Network Organ Sharing Registry. The primary outcome was patient survival from the date of orthotopic liver transplantation. Secondary outcomes included liver allograft survival and heart allograft survival. The study cohort included 301 CHLT recipients and six sequential heart-liver transplantation (SHLT) recipients. Patient survival after CHLT was 88% at 1 year, 84% at 3 years, and 82% at 5 years compared to 83%, 67%, and 50% in the SHLT group ($p = 0.010$). Liver allograft survival at 1, 3, and 5 years was 88%, 83% and 82%.

SUMMARY OF EVIDENCE

The evidence on CHLT includes registry studies that compared combined organ transplantation with heart or liver transplantation alone. Simultaneous heart and liver transplantation is feasible and was achieved in an extremely sick cohort of patients. CHLT in select patients with coexisting end-stage heart and liver failure appears to offer high survival and low rejection rates. The long-term survival rates are significant in a group of patients who have no other treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Organ Procurement and Transplantation Network

The Organ Procurement and Transplantation Network does not have a guidelines specific to combined heart-liver transplantation.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Currently there are no ongoing or unpublished clinical trials for a combined heart-liver transplantation.

Government Regulations

National:

No NCD available specific to combined heart-liver transplantation.

Local:

No LCD available specific to combined heart-liver transplantation.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Heart Transplant
- Heart-Lung Transplant
- Heart-Kidney Transplant
- Islet Transplantation
- Liver Transplant
- Lung and Lobar Lung Transplantation
- Pancreas Transplant
- Small Bowel and Liver/Multivisceral Transplant
- Small Bowel Transplant, Isolated

References

1. Atluri P, Gaffey A, Howard J, et al. Combined heart and liver transplantation can be safely performed with excellent short- and long-term results. *Ann Thorac Surg.* Sept 2014;98(3):858-62.
2. Careddu L, Zanfi C, Pantaleo A, Loforte A, et al. Combined heart-liver transplantation: a single-center experience. *Transpl Int.* Jul 2015;28(7):828-34.
3. Reich HJ, Awad M, Ruzza A, et al. Combined heart and liver transplantation: the Cedars-Sinai experience. *Transplant Proc.* Nov 2015;47(9):2722-6.
4. Beal EW, Mumtaz K, Hayes D, Whitson BA, Black SM. Combined heart-liver transplantation: indications, outcomes and current experience. *Transplant Rev.* Oct 2016;30(4):261-8.
5. Bryant R, Rizwan R, Zafar F, et al. Contemporary outcomes of combined heart-liver transplant in patients with congenital heart disease. *Transplantation.* Feb 2018;102(2):e67-e73.
6. Lebray P, and Varnous S. Combined heart and liver transplantation: state of the knowledge and outlooks. *Clin Res Hepatol Gastroenterol.* Apr 2019;42(2):123-130.
7. Vaikunth SS, Concepcion W, Daugherty T, et al. Short-term outcomes of en bloc combined heart and liver transplantation in the failing Fontan. *Clin Transplant.* Jun 2019;33(6):e13540.
8. Rizvi SS, Challapalli J, Maynes E, et al. Indications and outcomes of combined heart-liver transplant: a systematic review and met-analysis. *Transplant Rev.* Apr 2020;34(2):100517.
9. Yamaguchi Y, Burrier C, Roth C, Tumin D, et al. Sequential vs. combined heart-liver transplantation in the USA. *Dig Dis Sci.* Aug 2020;65(8):2427-2432.
10. Hanna RM, Kamgar M, Hasnain H, et al. Case report: first reported combined heart-liver transplant in a patient with a congenital solitary kidney. *Transplant Proc.* Apr 2018;50(3):943-946.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/21	4/20/21		Joint policy established
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)

Next Review Date: 2nd Qtr., 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: COMBINED HEART/LIVER TRANSPLANTATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy guidelines
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.