

# **Medical Policy Manual**

Transplant, Policy No. 18

# Small Bowel/Liver and Multivisceral Transplant

Effective: June 1, 2018

Next Review: March 2019 Last Review: April 2018

#### **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**

Small bowel/liver transplantation is performed in patients that have both intestinal and liver failure, and may be combined with the transplantation of other portions of the digestive tract and accessory organs.

# **MEDICAL POLICY CRITERIA**

- I. Candidates for all types of small bowel/liver or multivisceral transplant must meet both of the following criteria (A. and B.):
  - A. Adequate cardiopulmonary status
  - B. Documentation of patient compliance with medical management
- II. A small bowel/liver transplant or multivisceral transplant may be considered **medically necessary** for pediatric and adult patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who have been managed with long-term total parenteral nutrition and who have developed evidence of impending end-stage liver failure.
- III. A small bowel/liver transplant or multivisceral transplant may be considered **not medically necessary** when criterion I. or criterion II. is not met.

IV. A small bowel/liver retransplant or multivisceral retransplant may be considered **medically necessary** after a failed primary small bowel/liver transplant or multivisceral transplant.

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

### POLICY GUIDELINES

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. Liver Transplant, Transplant, Policy No. 5
- 2. Isolated Small Bowel Transplant, Transplant, Policy No. 9

# **BACKGROUND**

Small bowel/liver transplantation is transplantation of an intestinal allograft in combination with a liver allograft, either alone or in combination with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, or colon. Small bowel transplants are typically performed in patients with intestinal failure due to functional disorders (e.g., impaired motility) or short bowel syndrome, defined as an inadequate absorbing surface of the small intestine due to extensive disease or surgical removal of a large portion of small intestine.

In some instances, short bowel syndrome is associated with liver failure, often due to the long-term complications of total parenteral nutrition (TPN). These patients may be candidates for a small bowel/liver transplant or a multivisceral transplant, which includes the small bowel and liver with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, and/or colon. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant, and the patient requires removal of all of the native gastrointestinal tract and replacement with a multivisceral graft.

**Note:** Isolated small bowel transplants and isolated liver transplants are considered in separate medical policies (see Cross References section above).

# **EVIDENCE SUMMARY**

Much of the published literature consists of case series reported by single centers. Authors of these reports as well as narrative reviews observed that while outcomes continue to improve, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long term survival.

#### **REGISTRY DATA**

The most recent published report from the international Intestinal Transplant Registry (ITR) reported on 2887 transplants in 2699 patients from 82 transplant programs worldwide.<sup>[1]</sup>

Participation in this registry was considered to be nearly 100% of all intestinal transplants performed in the world since April 1985. The following results were reported:

- Regional practices and outcomes are now similar worldwide.
- Current actuarial patient survival rates at one-, five-, and 10-years post-transplant are 76%, 56%, and 43%, respectively.
- Outcomes of intestinal transplantation improved modestly over the past decade, but rates
  of graft loss beyond one year have not improved.
- The reasons for late graft loss have been difficult to identify due to the low case volumes at most centers.
- Better function was found in intestinal grafts that included a colon segment and/or a liver component.

Better graft survival was also seen in patients who waited at home for intestinal transplant, used induction immune-suppression therapy, and had rapamycin maintenance therapy.

#### NON-RANDOMIZED TRIALS

#### **Survival Outcomes**

The published literature consists of case series, mainly reported by single centers in the United States and Europe. Tables 1 and 2 summarize the characteristics and results of the case series, respectively. Many case series have included isolated small bowel transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off total parenteral nutrition (TPN). Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multivisceral transplants (see Table 2).

Several investigators have reported higher survival rates in transplants conducted more recently than those conducted earlier. [2-4] Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex procedure.

Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

Table 1. Summary of Key Case Series Characteristics for Transplantations<sup>[5]</sup>

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
				Treatment	n	
Lacaille (2017) <sup>[6]</sup>	France	110	5.3 (0.4-19)	<ul><li>Isolated IT</li><li>Combined liver IT</li><li>Multivisceral graft</li></ul>	45 60 5	Of 55 alive:  • 17 at <5 y  • 17 at 5-10 y  • 21 at ≥10 y
Garcia Aroz (2017) <sup>[7]</sup>	United States	10	1.5 (0.7-13)	Isolated IT     Combined liver IT	7 3	6/7 alive at follow-up ≥10 y

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
			, J.,,	Treatment	n	
Dore	United States	30	0.2	Isolated IT	6	28 (4-175) mo
(2016)[8]			(0.1-18)	<ul> <li>Combined liver IT</li> </ul>	6	
				<ul> <li>Multivisceral graft</li> </ul>	18	
Rutter	United	60	1.8	<ul> <li>Isolated IT</li> </ul>	16	21.3 (0-95) mo
(2016) <sup>[9]</sup>	Kingdom		(8-0)	<ul> <li>Multivisceral graft</li> </ul>	35	
				<ul> <li>Modified</li> </ul>	9	
				multivisceral		
Lauro	Italy	46	34	<ul> <li>Isolated IT</li> </ul>	34	51.3 mo
(2014) <sup>[10]</sup>			(NR)	<ul> <li>Combined liver IT</li> </ul>	6	
				<ul> <li>Multivisceral graft</li> </ul>	6	
Varkey	Sweden	20	Adults:	<ul> <li>Isolated IT</li> </ul>	4	NR
(2013)[11]			• 44 (20-67)	<ul> <li>Combined liver IT</li> </ul>	1	
			Children:	<ul> <li>Multivisceral graft</li> </ul>	15	
			• 6 (0.5-13)			
Mangus	United States	100	Adults:	<ul> <li>Multivisceral graft</li> </ul>	84	25 mo
(2013)[2]			• 48 (NR to 66)	Modified	16	
			Children:	multivisceral		
			• 1 (0.6 to NR)			

IT: intestinal transplantation; NR: not reported. <sup>a</sup> Living donors.

Table 2. Summary of Key Case Series Results for Transplantations<sup>[5]</sup>

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Lacaille	<ul> <li>Isolated IT</li> </ul>	60	● 59% at 10 y; 54% at 18 y	All treatments
(2017) <sup>[6]</sup>	<ul> <li>Combined liver IT</li> </ul>	45	• 48% at 10 y	combined:
	<ul> <li>Multivisceral graft</li> </ul>	5	• NR	<ul><li>73% at last follow-up</li></ul>
Garcia Aroz	Isolated IT	7	All transplantations	All treatments
(2017) <sup>[7]a</sup>	<ul> <li>Combined liver IT</li> </ul>	3	combined:	combined:
			• 70%	• 100% at last follow-up
Dore (2016) <sup>[8]</sup>	<ul> <li>Isolated IT</li> </ul>	6	● 83% at 9 y	All treatments
	<ul> <li>Combined liver IT</li> </ul>	6	● 33% at 10 y	combined:
	<ul> <li>Multivisceral graft</li> </ul>	18	● 67% at 2.5 y	• 71% in 31 d
				<ul> <li>62% at last follow-up</li> </ul>
Rutter	<ul> <li>Isolated IT</li> </ul>	16	● 92% at 1 y; 37% at 5 y	NR
(2016) <sup>[9]</sup>	<ul> <li>Multivisceral graft</li> </ul>	35	● 71% at 1 y; 33% at 5 y	
	Modified	9	● 85% at 1 y; 65% at 5 y	
	multivisceral			
Lauro	<ul> <li>Isolated IT</li> </ul>	34	All transplantations	NR
$(2014)^{[10]}$	<ul> <li>Combined liver IT</li> </ul>	6	combined:	
	<ul> <li>Multivisceral graft</li> </ul>	6	● 77% at 1 y	
			● 58% at 3 y	
			● 53% at 5 y	
			● 37% at 10 y	
Varkey	Isolated IT	4	All transplantations	NR
(2013) <sup>[11]</sup>	<ul> <li>Combined liver IT</li> </ul>	1	combined:	
	<ul> <li>Multivisceral graft</li> </ul>	15	● 78% at 1 y	
	_		● 50% at 5 y	

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Mangus (2013) <sup>[2]</sup>	Multivisceral graft     Modified     multivisceral	84 16	All transplantations combined: • 72% at 1 y • 57% at 5 y	NR

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

### **Complications**

Danziger-Isakov (2018) evaluated the epidemiology and outcomes of inpatient respiratory virus infection in pediatric patients following solid organ transplant at nine U.S. transplant centers. Among the 42 patients who underwent intestine/multivisceral transplantation, respiratory virus infection occurred in 38%, the highest rate by transplant type. Respiratory virus infection was associated with younger age at transplant.

Vo (2018) reported on the risk of invasive pneumococcal infections among pediatric patients receiving liver-small bowel-pancreas transplants at a single center.<sup>[13]</sup> Of the 122 patients who underwent this procedure between 2008 and 2016, nine patients experienced 12 invasive pneumococcal infections. The median time to first infection following transplant was three years (range 0.8 to 5.8 years), and the mortality rate was 22%. The authors noted that all patients were on prophylactic oral penicillin and the majority had received at least one dose of pneumococcal conjugate vaccine.

Nagai (2016) reported on cytomegalovirus (CMV) infection after intestinal or multivisceral transplantation at a single center in the US.<sup>[14]</sup> A total of 210 patients had in intestinal transplant, multivisceral transplant or modified multivisceral transplant between January 2003 and June 2014. The median length of follow-up was 2.1 years. A total of 34 patients (16%) developed CMV infection a median of 347 days after transplantation. Nineteen patients had tissue invasive CMV disease. CMV infection was significantly associated with rejection (odds ratio 2.6, p<0.01) and adversely affected patient survival (hazard ratio 2.7, p<0.001). A report from another center in the US, 16 of 85 (19%) patients undergoing intestinal or multivisceral transplantation developed CMV infection a mean of 139 days (range 14 to 243 days) postoperatively.<sup>[15]</sup>

Wu (2016) investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (n=175). [16] Acute ABMR was diagnosed by: clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free grafts, 36% included a liver graft, and 6.3% were retransplantations. Eighteen cases of acute ABMR were identified—14 (14%) among the patients undergoing first liver-free transplantation, two (3%) among patients undergoing liver/small bowel transplantations, and two (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

In a case series by Cromvik (2016), five of 26 patients (19%) were diagnosed with graft-versus-host disease (GVHD) after intestinal or multivisceral transplantation at a center in

<sup>&</sup>lt;sup>a</sup> Living donors.

Sweden.<sup>[17]</sup> Risk factors for GVHD were malignancy as a cause of transplantation and neoadjuvant chemotherapy or brachytherapy before transplantation.

A 2015 retrospective review reported a number of parameters for intestinal and multivisceral transplants performed on Nordic patients between 1998 and 2013. [18] Twenty out of the 29 patients (69%) received liver-containing allografts. Nineteen of them were multivisceral grafts, including the stomach, the pancreaticoduodenal complex, the liver and the small intestine. The remaining liver-containing allograft was a combined liver and intestinal graft with a segmental pancreas. Three of eight patients with a spleen included in their multivisceral graft developed GVHD. One patient with GVHD and manifestations with skin rash later developed post-transplant lymphoproliferative disorder (PTLD).

A 2012 retrospective review focused on the rate of kidney dysfunction, a recognized complication after non-renal solid organ transplantation, in 33 multivisceral and 15 isolated small bowel transplant patients. [19] A significant decline in kidney function was reported in 46% of patients at one year following transplantation. A significant correlation was found for patient age, pretransplant serum creatinine, estimated GFR (eGFR) at post-transplant day 30, 90, 180, and 270, and tacrolimus level at post-transplant day seven. Lesser decline was found in pediatric patients and patients with multivisceral transplantation compared with adults or isolated small bowel transplantation.

A 2012 retrospective review reported on bloodstream infections among 98 children younger than age 18 years with small bowel/combined organ transplants. [20] Seventy-seven (79%) patients underwent small bowel transplant in combination with a liver, kidney, or kidney-pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients remained alive. The one-year survival rate was similar in patients with combined small bowel transplant (75%) and those with isolated small bowel transplant (81%). In the first year after transplantation, 68 patients (69.4%) experienced at least one episode of bloodstream infection. The 1-year survival rate for patients with bloodstream infections was 72% compared to 87% in patients without bloodstream infections (p-value= 0.056 for difference in survival in patients with and without bloodstream infections).

Wu (2011) reported on complications after small bowel and multivisceral transplantation in 241 patients who underwent intestinal transplantation. Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants and 12% had small bowel/liver transplants. There were 151 children (63%) and 90 adults. A total of 22 patients (9%) developed graft-versus-host disease (GVHD). Children younger than five years old were more likely to develop GVHD; the incidence in this age group was 16 of 121 (13.2%) compared to 2 of 30 (6.7%) in children between 5 and 18 years and 9 of 90 (4.4%) in adults over 18 years. Among diseases, patients with intestinal atresia were more likely to develop GVHD than those with other conditions (22.2% vs. 2.6%, respectively; p=0.03).

### **Transplant Recipients with Malignancies**

Cruz (2011) published results from a small case series (n=10) of patients with intra-abdominal desmoid tumors secondary to familial adenomatous polyposis who underwent multivisceral transplant. [22] All patients were able to discontinue home parenteral nutrition by an average 30 days after transplant. Estimated survival was 80% at five years, and desmoid tumors reoccurred in one patient 15 months after transplantation. However, conclusions from this study are limited by the small sample size and the lack of a comparison group, factors which do not allow for the isolation of transplant as a causative factor in patient health outcomes.

### **HIV Positive Transplant Recipients**

The subgroup of HIV positive transplant recipients has been controversial due to the long-term prognosis for HIV positivity, the impact of immunosuppression on HIV disease, and the interactions of immunosuppressive therapy on HIV disease. Although HIV positive transplant recipients may be a research interest of some transplant centers, the minimal data regarding long term outcomes in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease. "The OPTN permits HIV test positive individuals as organ candidates if permitted by the transplant hospital. Care of HIV test positive organ candidate and recipients should not deviate from general medical practice." [23]

# Retransplantation

Evidence for the use of retransplantation to treat individuals who have failed intestinal transplantations includes several case series, mostly from single institutions. One case series analyzed records from the United Network for Organ Sharing database.<sup>[4]</sup> Among the case series described in Table 3, reasons for retransplantation include: acute rejection, chronic rejection, CMV, liver failure, lymphoproliferative disorder, and graft dysfunction. Survival rates for retransplantation are listed in Table 4.

Table 3. Summary of Key Case Series Characteristics for Retransplantation<sup>[5]</sup>

Author (Year)	Location	N	Median Age (Range), y		Interventions	
				Treatment	n	
Kubal	United	23	27	<ul> <li>Isolated IT</li> </ul>	1	NR
$(2018)^{[24]}$	States		(1-58)	<ul> <li>Multivisceral graft</li> </ul>	22	
Lacaille	France	10	13	• Isolated IT	3	4
$(2017)^{[6]}$			(5-16)	<ul> <li>Combined liver IT</li> </ul>	7	
Desai	United	• 72 (adults)	NR	Adults:		NR
(2012)[4]	States	• 77		<ul> <li>Isolated IT</li> </ul>	41	
		(children)		<ul> <li>Combined liver IT</li> </ul>	31	
				Children:		
				<ul> <li>Isolated IT</li> </ul>	28	
				<ul> <li>Combined liver IT</li> </ul>	49	
Abu-Elmagd	United	47	NR	<ul> <li>Isolated IT</li> </ul>	31	NR
(2009) <sup>[3]</sup>	States			<ul> <li>Combined liver IT</li> </ul>	7	
				<ul> <li>Multivisceral graft</li> </ul>	9	
Mazariegos	United	14	9.4	• Isolated IT	1	55.9
$(2008)^{[25]}$	States		(3.2-22.7)	<ul> <li>Combined liver IT</li> </ul>	3	
				<ul> <li>Multivisceral graft</li> </ul>	10	

IT: intestinal transplantation; NR: not reported.

Table 4. Summary of Key Case Series Results for Retransplantation<sup>[5]</sup>

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Kubal (2018)[24]	• Isolated IT	1	All transplantations combined:	NR
	<ul> <li>Multivisceral graft</li> </ul>	22	● 34% at 1 y	

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Lacaille (2017) <sup>[6]</sup>	<ul> <li>Isolated IT</li> </ul>	3	All transplantations combined:	NR
	<ul> <li>Combined liver IT</li> </ul>	7	• 30% at last follow-up	
Desai (2012) <sup>[4]</sup>	Adults:		Adults:	NR
	<ul> <li>Isolated IT</li> </ul>	41	● 80% at 1 y; 47% at 3 y; 29% at 5 y	
	<ul> <li>Combined liver IT</li> </ul>	31	● 63% at 1 y; 56% at 3 y; 47% at 5 y	
	Children:		Children:	
	<ul> <li>Isolated IT</li> </ul>	28	● 81% at 1 y; 74% at 3 y; 57% at 5 y	
	<ul> <li>Combined liver IT</li> </ul>	49	● 42% at 1 y; 42% at 3 y; 42% at 5 y	
Abu-Elmagdl (2009)[3]	<ul> <li>Isolated IT</li> </ul>	31	All transplantations combined:	NR
	<ul> <li>Combined liver IT</li> </ul>	7	● 69% at 1 y	
	<ul> <li>Multivisceral graft</li> </ul>	9	● 47% at 5 y	
Mazariegos (2008)[25]	Isolated IT	1	All transplantations combined:	100%
	<ul> <li>Combined liver IT</li> </ul>	3	• 71% at last follow-up	
	<ul> <li>Multivisceral graft</li> </ul>	10		

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

# PRACTICE GUIDELINE SUMMARY

#### AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2003, the American Gastroenterological Association published a position statement on short bowel syndrome and intestinal transplantation. The statement noted that only patients with life-threatening complications due to intestinal failure or long-term total parenteral nutrition have undergone intestinal transplantation. The statement recommended the following Medicare-approved indications, pending availability of additional data:

- Impending liver failure
- Thrombosis of major central venous channels
- Frequent central line associated sepsis
- Frequent severe dehydration.

# **SUMMARY**

There is enough research to show that small bowel/liver and multivisceral transplant and retransplant can improve survival in certain patients. Therefore, these procedures may be considered medically necessary for patients with intestinal failure who have been managed with long-term total parenteral nutrition and who have developed evidence of impending end-stage liver failure. Transplants or retransplants are considered not medically necessary when the policy criteria are not met.

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		CODES
Codes	Number	Description
CPT	43999	Unlisted procedure, stomach
	44132	Donor enterectomy, (including cold preservation) open; from cadaver donor
	44133	Donor enterectomy, (including cold preservation) open; partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
	44799	Unlisted procedure, small intestine
	47133	Donor hepatectomy, (including cold preservation) from cadaver donor

Codes	Number	Description
	47135	Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	;total left lobectomy (segments II, III and IV)
	47142	;total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	;with trisegment split of whole liver graft into 2 partial liver grafts (ie, left lateral segment [segments I and III] and right trisegment [segments I and IV through VIII])
	47145	;with lobe split of whole liver graft into 2 partial liver grafts (ie, left lobe [segments I, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
	48999	Unlisted procedure, pancreas
HCPCS	S2053	Transplantation of small intestine, and liver allografts
	S2054	Transplantation of multivisceral organs
	S2055	Harvesting of donor multivisceral organs, with preparation and maintenance of allografts; from cadaver donor
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre and posttransplant care in the global definition

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