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Transforming Transplant Oversight: Enhancing Combined Cardiothoracic Surgery and Liver Transplantation With Normothermic Machine Perfusion

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Background. Simultaneous cardiothoracic surgery and liver transplantation (LT) is a high-risk procedure associated with high mortality and morbidity rates. The use of normothermic machine perfusion (NMP) allows graft quality enhancement, assessment of liver viability, and logistics optimization, expanding the donor pool and reducing organ discard rate. We share our institution's experience with simultaneous cardiothoracic surgery and LT, using NMP for liver graft preservation and viability assessment. **Methods.** Data was retrospectively collected from 14 patients who underwent simultaneous cardiothoracic surgery and LT with NMP for liver graft preservation from October 2022 to August 2023. Data was divided into 3 groups: combined heart transplant and LT, lungs transplant and LT, and nontransplant cardiothoracic surgery and LT. **Results.** All liver grafts were from brain-dead donors. Median machine perfusion times were 211 min (range, 186–242 min), 222 min (range, 211–246 min), and 627 min (range, 180–1003 min) across the 3 groups, respectively. Postreperfusion syndrome occurred in 3 patients (21%), with 5 (36%) readmitted within 30 d because of complications. Biliary complications developed in 5 patients (36%), and 2 (14%) experienced acute liver rejection within 90 d postsurgery. No mortality was recorded during the median 18-mo follow-up. **Conclusions.** NMP serves as a safe and valuable tool for patients in need of simultaneous cardiothoracic surgery and LT, potentially broadening the scope of eligibility for these complex procedures.

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Liver transplantation is acknowledged as a definite treatment for end-stage liver disease. However, the presence of significant cardiopulmonary conditions frequently makes such patients ineligible for liver transplantation alone.[1-3] The integration of combined cardiothoracic surgical procedures with liver transplantation has opened the door for these patients to

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**In organ donation, "expedite organ placement" refers to a method of allocation aimed to quickly place organs that have been declined late during recovery and are therefore at risk of not being used for transplant.*

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become suitable candidates. This includes simultaneous coronary artery bypass grafting, valve repair or replacement, heart transplantation, and lung transplantation, thereby expanding the therapeutic options for patients with concurrent end-stage liver disease and severe cardiopulmonary diseases.[3-5] However, combined cardiothoracic surgery and liver transplantation is highly complex and challenging and is characterized by considerable morbidity and mortality rates. Understandably, given limited experience with these combined procedures,[3,6,7] careful consideration in the selection of suitable donor organs is essential. The use of extended criteria donors (ECDs) with marginal liver function is generally discouraged to minimize the risks associated with combined surgeries. However, this practice of prioritizing organs from low-risk donors[1] can contribute to prolonged waitlist times and increase the likelihood of patients deteriorating or dying before a transplant can occur. Additionally, the complexity of undertaking combined cardiothoracic surgery and liver transplantation is significantly increased by the prolonged cold ischemia time (CIT) of liver allografts. This is primarily a consequence of the procedural sequence, wherein liver transplantation is performed after the cardiothoracic procedures. As a result, even when using organs from low-risk donors, prolonged CIT may lead to significant hemodynamic instability upon unclamping of the portal vein.[8] Thus, identifying strategies to minimize the risks of intraoperative hemodynamic instability is imperative for patients undergoing combined cardiothoracic surgery and liver transplantation.

Machine perfusion technologies, including normothermic machine perfusion (NMP) and hypothermic oxygenated machine perfusion, has been a breakthrough innovation of the early 21st century for liver transplantation.[9-12] Its clinical use supports enhanced graft quality, assessment of liver viability, and logistics optimization, expanding the donor pool and reducing organ discard rate.[13-16] Since October 2022, our institution has programmatically implemented NMP for liver transplantation as the standard of care. This report reviews our initial experience with NMP in 14 liver transplant recipients who also underwent simultaneous cardiothoracic surgery, such as heart transplant, double-lung transplant, and nontransplant heart surgery.

MATERIALS AND METHODS

Patients

This retrospective case series examines 14 adult patients who received simultaneous cardiothoracic surgery and liver transplant at Cleveland Clinic, Ohio, from October 2022 to August 2023. Liver preservation was achieved through OrganOx Metra for normothermic ex situ perfusion, with cardiothoracic surgeries preceding liver transplants. Procedures included heart transplants, double-lung transplants, coronary artery bypass grafting, pericardiectomy, tricuspid, and aortic valve repairs. This study was approved by the Cleveland Clinic's Institutional Review Board (IRB No. 18-1167).

Ex Situ Normothermic Machine Perfusion

Liver grafts were recovered in a standard fashion, stored in cold Histidine-Tryptophan-Ketoglutarate solution, and transported to our Center. After back-table preparation, grafts were cannulated, primed with albumin solution, and connected to the OrganOx Metra device, using the previously prepared perfusate containing albumin, packed red blood cells, heparin, ceftriaxone, calcium gluconate, and sodium bicarbonate. During NMP, graft viability was monitored by assessing perfusion parameters—such as arterial and venous flow and pressure—perfusate pH and lactate clearance, and bile flow and chemistry, including bile pH, bicarbonate, and glucose. Samples were taken before connection to the Metra device and at set intervals to check baseline and ongoing perfusate metrics. Recorded times included CIT, NMP duration, recipient warm ischemia time, and total preservation time. Post-NMP, grafts were flushed with cold Histidine-Tryptophan-Ketoglutarate and during liver implantation with saline.

Statistical Analysis

Continuous variables were presented as median and range and compared using the Kruskal-Wallis test. Dichotomous variables were assessed with a chi-square test. JMP Pro, Version 16.1.0, was used to analyze the data, with $P < 0.05$ considered significant. Figures 1-2 are obtained using GraphPad Prism version 10.2.0 for Mac (GraphPad Software, Boston, MA, www.graphpad.com).

RESULTS

Recipient and Donor Demographics

Table 1 summarizes recipient and donor characteristics. Heart and liver transplant recipients were younger, with a median age of 38 y (range, 27–43 y), compared with lung and liver transplant recipients (55.5 y; range, 47–63 y) and those having nontransplant cardiac surgery with liver transplant (66 y; range, 43–70 y; $P < 0.05$). The median waitlist time for combined cardiothoracic surgery/liver transplantation recipients was 26.5 d (range, 3–487 d), varying significantly among groups: 9 d (range, 3–487 d) for liver/heart transplant, 59.5 d (range, 50–327 d) for liver/lung transplant, and 19.5 d (range, 5–218 d) for liver/nontransplant cardiac surgery with liver transplant. The underlying liver diseases were Fontan-associated liver disease (n = 2), metabolic dysfunction-associated steatohepatitis (n = 2), short telomere syndrome (n = 3), alcoholic cirrhosis (n = 5), cryptogenic cirrhosis (n = 1), congestive hepatopathy because of cardiac cirrhosis (n = 1), hepatitis B or C virus cirrhosis (n = 4), and alpha-1 antitrypsin deficiency. Liver cancer was present in 2 patients: 1 patient had hepatocellular carcinoma and another had cholangiocarcinoma. All patients exhibited clinical signs of portal hypertension, which included splenomegaly (n = 7), esophageal varices (n = 11), ascites (n = 14), and hepatic encephalopathy (n = 6). The median laboratory Model for End-Stage Liver Disease score at transplant was 17 (range, 9–27) for the group undergoing heart transplantation. For the lung transplant group, the median Model for End-Stage Liver Disease score was 10 (range, 7–14), lower than that of the nontransplant cardiac surgery group, which was 23 (range, 18–26) but not statistically significant ($P = 0.054$). Before transplant, 2 patients (50%) of the heart-liver recipients had acute kidney injury (AKI). In the nontransplant cardiac surgery group, 1 patient (17%) had AKI and 3 patients (50%) had chronic kidney disease stage 3, with 1 needing dialysis. Eight patients (57%), including all heart, 2 lung, and 2 nontransplant cardiac surgery patients, were hospitalized and required intensive care unit (ICU) stays presurgery. ICU admissions were mainly for

TABLE 1.

Recipient and donor characteristics

Recipients

Type of surgery	Case no.	Indication for LT	Indication for CTS	Type of CTS	Age (y)	Sex	BMI (kg/m²)	MELD at transplant	eGFR (mL/min/1.73 m²)	Waitlist time (d)	Preoperative status
Heart-liver transplant	1	Congestive hepatopathy	Hypertrophic cardiomyopathy	Heart Tx	43	F	27	27	95	3	ICU
	2	Cryptogenic cirrhosis	Restrictive cardiomyopathy	Heart Tx	27	M	28	23	42	8	ICU
	3	FALD	Failed Fontan	Heart Tx	33	F	27	11	117	487	ICU
	4	FALD	Failed Fontan	Heart Tx	43	F	21	9	59	10	ICU
Median					38		27	17	77	9	
Lung-liver transplant	5	HBV cirrhosis	Sarcoidosis	Lung Tx	49	M	23	12	97	69	Home
	6	Short telomere SD	IPF	Lung Tx	62	F	19	7	71	327	Home
	7	Short telomere SD	IPF	Lung Tx	47	M	26	14	113	21	ICU
	8	MASH, short telomere SD	IPF	Lung Tx	63	M	32	8	107	50	ICU
Median					55.5		24.5	10	102	59.5	
Heart surgery and liver transplant	9	Alcohol cirrhosis, HCV, CCA	CAD	CABG	68	M	28	26	78	218	Home
	10	Alcohol cirrhosis, HCV, HCC	CAD	CABG	70	F	24	24	64	85	Home
	11	MASH	CAD	CABG	64	M	26	22	38	32	Home
	12	Alcohol cirrhosis, A1AT heterozygosity	Constrictive pericarditis	Pericardiectomy	43	M	27	26	60	5	ICU
	13[a]	Alcohol cirrhosis, HCV cirrhosis	Tricuspid regurgitation	TV repair	68	M	27	22	44[b]	7	ICU
	14	Alcohol cirrhosis	endocarditis	AVR, TV repair	53	M	28	18	105	7	Home
Median					66		27	23	62	19.5	
P[c]					0.018		0.626	0.054	0.2	0.443	

Donors

Type of surgery	Case no.	Age (y)	Sex	BMI (kg/m²)	Peak ALT (U/L)	Peak AST (U/L)	Peak total bilirubin (mg/dL)	End ALT[d] (U/L)	End AST[d] (U/L)	Liver biopsy	DRI	No. of pressors during procurement	Expedited open offer[e]
Heart-liver transplant	1	38	M	28	80	127	0.9	57	96	Normal	1.22	0	
	2	22	M	22	51	81	1.5	23	35	Normal	1.17	2	
	3	34	M	25	112	284	1.7	81	93	Focal periportal fibrosis	1.11	0	
	4	34	F	26	106	484	0.7	64	447	Normal	1.38	0	
Median		34		25.5	93	205.5	1.2	60.5	94.5		1.20		
Lung-liver transplant	5	42	M	23	20	37	0.9	20	25	Normal	1.7	0	
	6	45	F	25	797	826	1.5	265	380	Normal	1.92	1	
	7	46	M	29	35	54	4.3	35	28	Focal necrosis, periportal fibrosis	1.69	0	
	8	56	M	29	92	38	0.6	47	21	Normal	1.81	1	
Median		45.5		27	63.5	46	1.2	41	26.5		1.76		

(Continued)

TABLE 1.
continued

Donors													
Type of surgery	**Case no.**	**Age (y)**	**Sex**	**BMI (kg/m²)**	**Peak ALT (U/L)**	**Peak AST (U/L)**	**Peak total bilirubin (mg/dL)**	**End ALT[d] (U/L)**	**End AST[d] (U/L)**	**Liver biopsy**	**DRI**	**No. of pressors during procurement**	**Expedited open offer[e]**
Heart surgery and liver transplant	9	59	F	27	20	15	1.6	20	11	Normal	1.94	1	
	10	11	M	31	17	113	0.8	14	113	10% Mac-S	1.08	3	Yes
	11	42	M	31	5143	5164	0.4	472	80	15% Mac-S, confluent necrosis, portal and periportal fibrosis	1.61	0	
	12	28	F	23	12	40	0.3	12	40	Patchy necrosis, patchy perisinusoidal fibrosis	1.57	0	Yes
	13	48	F	26	36	49	0.2	27	20	Normal	1.61	0	
	14	64	F	45	54	48	3.8	52	48	Normal	2.1	0	Yes
Median		45		29	28	48.5	0.6	23.5	44		1.61		
P[b]		0.161		0.302	0.326	0.297	0.506				0.053		

[a]This patient underwent a kidney transplant the following day from the same deceased donor.
[b]This patient was on CRRT before surgery.
[c]A *P* value of <0.05 is considered significant.
[d]Upon organ acceptance.
[e]Accepted after cross-clamp.
A1AT, alpha-1 antitrypsin; ALT, alanine transaminase; AST, aspartate aminotransferase; AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCA, cholangiocarcinoma; CRRT, continuous renal replacement therapy; CTS, cardiothoracic surgery; DRI, donor risk index; eGFR, estimated glomerular filtration rate; F, female; FALD, Fontan-associated liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; ; IPF, idiopathic pulmonary fibrosis; LT, liver transplantation; M, male; Mac-S, macrovesicular steatosis; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-stage Liver Disease; SD, syndrome; TV, tricuspid valve; Tx, transplant.

cardiopulmonary issues, including heart failure (n = 4), pulmonary hypertension (n = 1), hypoxemia (n = 2), and hepatic encephalopathy (n = 1).

All 14 liver grafts were from brain-dead donors, with a median age of 42 y (range, 11–64 y). The overall median donor risk index (DRI) was 1.61 (range, 1.08–2.1). Heart transplant recipients had donors with a lower median DRI of 1.2 (range, 1.11–1.38), versus lung transplant (median DRI, 1.76; range, 1.7–1.92) and heart surgery recipients (median DRI, 1.61; range, 1.08–2.1). Liver biopsy from 5 grafts (36%) revealed a range of histological abnormalities, including periportal fibrosis (n = 3), perisinusoidal fibrosis (n = 1), parenchymal necrosis with or without confluence involvement (n = 3), and mild macrovesicular steatosis (n = 2, 10% and 15%). In the heart transplant group, the median peak donor alanine transaminase (ALT) was 93 U/L (range, 51–112 mg/dL) and aspartate transaminase (AST) was 205.5 U/L (range, 81–484 mg/dL), with bilirubin at 1.2 mg/dL (range, 0.7–1.7 mg/dL). For lung transplants, the median peak ALT was 63.5 U/L (range, 35–797 mg/dL) and AST was 46 U/L (range, 37–826 mg/dL), with bilirubin at 1.2 mg/dL (range, 0.6–4.3 mg/dL). The nontransplant cardiac surgery group had median peak ALT 28 U/L (range, 12–5143 mg/dL) and median peak AST was 48.5 U/L (range, 15–5164 mg/dL), with bilirubin at 0.6 mg/dL (range, 0.2–3.8 mg/dL). Half (50%) of the donors in this group were accepted as expedited open offers after cross-clamp.*

Organ Preservation and Recipient Surgery

Table 2 details organ preservation and recipient operation specifics. NMP time with nontransplant cardiac surgery has the longest median at 10.45 h (range, 3–16.7 h; $P = 0.09$). The median CIT for liver grafts before NMP was similar across the groups. No machine perfusion was used for heart or lung grafts.

Figure 1A shows lactate clearance during NMP in perfusate, starting before liver connection at a median of 12.92 mmol/L (range, 7.22–16.13 mmol/L), dropping to 0.6 mmol/L (range, 0.29–2.79 mmol/L) within an hour and 0.54 mmol/L (range, 0.29–3.62 mmol/L) by hour 2. Figure 1B indicates all liver grafts produced bile at a median rate of 10.5 mL/h (range, 2–27 mL/h) with a median bile pH of 7.78 (range, 7.72–7.84) throughout NMP.[17] Seven patients (50%) required cardiopulmonary bypass, including those undergoing heart transplants (n = 4), aortic valve replacement with tricuspid valve repair (n = 1), tricuspid valve repair (n = 1), and pericardiectomy (n = 1). All patients remained stable and were weaned off cardiopulmonary bypass before liver transplantation. For all lung-liver transplants, venoarterial extracorporeal membrane oxygenation was used but discontinued before liver transplantation. During liver transplant, 3 patients (21%) had postreperfusion syndrome (PRS), marked by a 30% or more drop in mean arterial pressure from baseline after liver graft reperfusion.[8] Two of these patients were in the heart transplant group and 1 was in the nontransplant cardiac surgery group (**Figure S1, SDC**, https://links.lww.com/TXD/A765). There were no intraoperative deaths. Notably, patient number 13 underwent liver and tricuspid valve repair and received a kidney graft from the same donor the next day.

Postoperative Outcomes

Postoperative outcomes are detailed in Table 3. Two patients (14%) had peak ALT levels >1000 IU/L in the first

TABLE 2.

Organ preservation and recipient surgery

Type of surgery	Case no.	Heart or lung CIT (min)	Liver CIT[a] (min)	NMP duration (min)	Recipient WIT (min)	Total operation time (min)	PRBC (units)	PLT (units)	FFP (units)	Cryo (units)	CP bypass	V-A ECMO
Heart-liver transplant	1	173	324	186	46	820	15	8	10	4	Yes	No
	2	146	299	215	38	952	9	3	7	3	Yes	No
	3	227	301	242	40	1112	6	11	10	6	Yes	No
	4	210	302	207	30	890	7	5	6	6	Yes	No
Median or N (%)		191.5	301.5	211	39	921	8	6.5	8.5	5	4 (100%)	0
Lung-liver transplant	5	L: 223; R: 329	313	246	39	1000	2	3	0	2	No	Yes
	6	L: 187; R: 245	373	160	43	728	9	4	3	4	No	Yes
	7	L: 326; R: 394	470	233	59	892	8	7	4	6	No	Yes
	8	L:310; R: 395	428	211	38	840	2	2	0	0	No	Yes
Median or N (%)		L: 266.5; R: 361.5	400.5	222	41	866	5	3.5	1.5	3	0	4 (100%)
Heart surgery and liver transplant	9	N/A	380	751	35	640	7	1	2	2	No	No
	10	N/A	261	180	31	651	4	2	3	2	No	No
	11	N/A	383	704	27	935	16	10	13	10	No	No
	12	N/A	440	550	35	838	21	10	10	6	Yes	No
	13[b]	N/A	403	547	40	755	11	9	15	6	Yes	No
	14	N/A	378	1003	37	982	15	12	14	8	Yes	No
Median or N (%)			381.5	627	35	796.5	13	9.5	11.5	6	3 (50%)	0
P[c]			0.101	0.09	0.096	0.382	0.193	0.442	0.061	0.36		

[a]Before normothermic machine perfusion.

[b]This patient underwent a kidney transplant the following day from the same deceased donor.

[c]A *P* value of <0.05 is considered significant.

CIT, cold ischemia time; CP, cardiopulmonary; cryo, cryoprecipitate; FFP, fresh frozen plasma; L, left; N/A, not applicable; NMP, normothermic machine perfusion; PLT, platelets; PRBC, packed red blood cells; R, right; V-A ECMO, venoarterial extracorporeal membrane oxygenation; WIT, warm ischemia time.

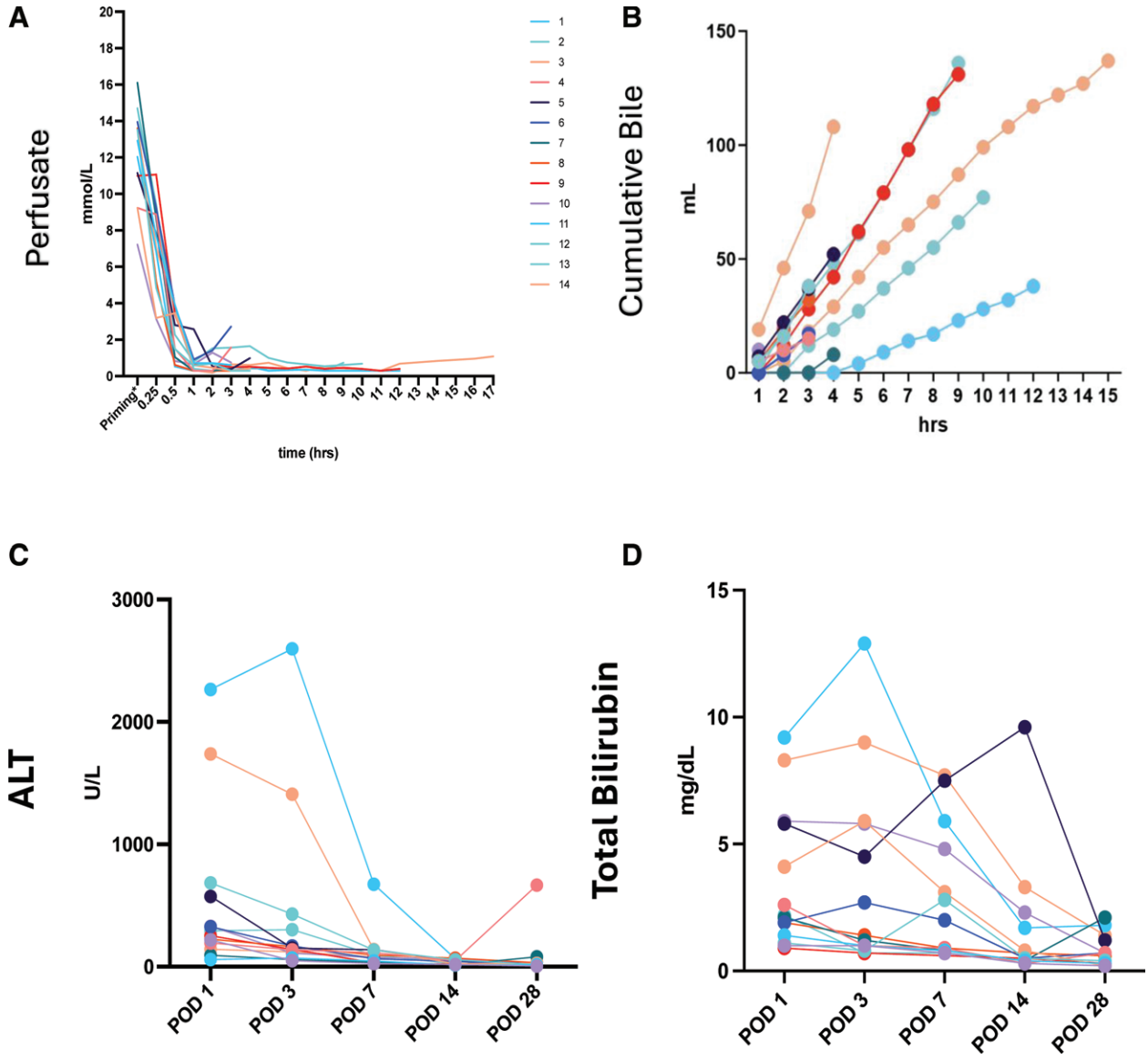

FIGURE 1. Lactate clearance during NMP. *Refers to the priming phase, before connection of the graft (A). Cumulative bile production during NMP (B). Bile production was not recorded for liver number 1. Changes in ALT (C) and total bilirubin level (D) after transplant. AST, aspartate transaminase; NMP, normothermic machine perfusion; POD, postoperative day.

week posttransplant, but the median ALT dropped to 46 IU/L (range, 14–69 IU/L) by day 14 (Figure 1C). Median bilirubin levels were 0.5 mg/dL (range, 0.3–9.6 mg/dL) on day 14 and 0.65 mg/dL (range, 0.2–2.1 mg/dL) on day 28 (Figure 1D). Two patients (7%) had early allograft dysfunction (EAD) because of high transaminases. Postsurgery, 11 patients (79%) developed 1 or more cardiopulmonary complications, including arrhythmias (n = 7), low ejection fraction (n = 3), pleural (n = 1) and pericardial effusion (n = 2), respiratory failure (n = 6), and >7 d of ventilation support (n = 1). Four patients (29%) needed surgical exploration of a thoracic incision (n = 2) for mediastinal bleeding and abdominal exploration for hepatic artery stenosis (n = 1) and wound dehiscence (n = 1). Nine patients (64%) developed AKI, defined by the 2012 Kidney Disease: Improving Global Outcomes guidelines, with 2 patients requiring hemodialysis. The duration of stay in the ICU and hospital varied between the 3 groups. The hospital stay in patients with nontransplant cardiac surgery (median, 15 d; range, 10–20 d) was significantly shorter than hospital stays among heart and lung recipients (median for heart recipients was 58 d; range, 16–185 d and median for lung recipients was 40 d [range, 27–126 d; $P < 0.05$]). Five patients (36%) were readmitted because of cardiac (n = 1) or noncardiac (n = 4) complications within 30 d after discharge from their index transplants. Over the median follow-up period of 556 d (range, 434–740 d), 5 patients (36%) developed a biliary anastomotic stricture, which was successfully managed with a biliary stent, including 1 patient with ischemic cholangiopathy. Biopsy-proven acute cellular rejection of the liver, heart, and lungs occurred in 2 (14%), 3 (75%), and 3 (75%) patients, respectively. Two patients developed acute cellular rejection after 90 d posttransplant. According to the Clavien-Dindo classification (**Table S1, SDC**, https://links.lww.com/TXD/A765), 10 patients (71%) experienced complications of grade IIIb or higher. No case of primary nonfunction was recorded, and as of the most recent follow-up, the patient who

TABLE 3.

Posttransplant outcomes

						Peak laboratory values within 7 d after transplant				Acute rejection[b]					
	Case no.	ICU stay (d)	Hospital stay (d)	PRS[a]	EAD	Lactate (mmol/L)	AST (IU/L)	ALT (IU/L)	Total bilirubin	Heart or lung	Liver	Biliary complications	Vascular complications	AKI (KDIGO stage)	Follow-up (mo)
Heart-liver transplant	1	10	25	Yes	No	1.4	405	219	1	No	No	No	No	No	25
	2	6	16	No	No	6	202	72	1.4	Yes	Yes	No	No	Yes (II)	24
	3	3	91	No	No	2.4	1890	685	2.8	Yes	No	No	No	Yes (II)	15
	4	22	185	Yes	Yes	2.6	5694	1739	5.9	Yes	No	No	HA stenosis	Yes(I)	15
Median or N (%)		8	58	2 (50%)	1 (25%)	2.5	1147.5	452	2.1	3 (75%)	1 (25%)	0	1 (25%)	3 (75%)	
Lung-liver transplant	5	21	41	No	No	2.5	363	193	2.6	Yes	No	AS	No	Yes (III)	20
	6	2	39	No	No	3.1	924	574	7.9	Yes	No	AS	No	Yes (III)	19
	7	9	27	No	No	1.4	280	326	2.9	No	No	No	No	Yes (II)	18
	8	9	126	No	No	2.5	151	94	2.1	Yes	Yes	AS	No	Yes (III)	17
Median or N (%)		9	40	0	0	2.5	321.5	259.5	2.75	3 (75%)	1 (25%)	3 (75%)	0	4 (100%)	
Heart surgery and liver transplant	9	12	15	No	No	1.6	346	224	1.9	N/A	No	AS	No	No	23
	10	8	10	No	No	1.3	420	253	0.9	N/A	No	No	No	Yes (II)	21
	11	12	14	No	No	3.2	872	330	6.2	N/A	No	AS	No	Yes (III)	20
	12	7	20	No	Yes	6.4	4863	2821	12.9	N/A	Yes	NAS	No	No	18
	13	2	19	No	No	2.9	651	307	2.2	N/A	No	No	No	Yes (I)	17
	14	6	15	Yes	No	3.1	365	144	9	N/A	Yes	No	No	Yes (III)	16
Median or N (%)		7.5	15	1 (17%)	1 (17%)	3	535.5	280	4.2		2 (33%)	3 (50%)	0	4 (67%)	18
P[c]		0.927	0.017	0.211	0.586	0.759	0.364	0.849	0.612			0.09		0.752	

[a]Defined as a decrement of the MAP ≥ 30% of the baseline MAP value, that lasts for at least 1 min, in the first 5 min after liver reperfusion.

[b]Biopsy proven.

[c]A *P* value of <0.05 is considered significant.

AKI, acute kidney injury; ALT, alanine transaminase; AS, anastomotic stricture; AST, aspartate aminotransferase; EAD, early allograft dysfunction of liver grafts; HA, hepatic artery; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; NAS, nonanastomotic biliary stricture; PRS, postreperfusion syndrome.

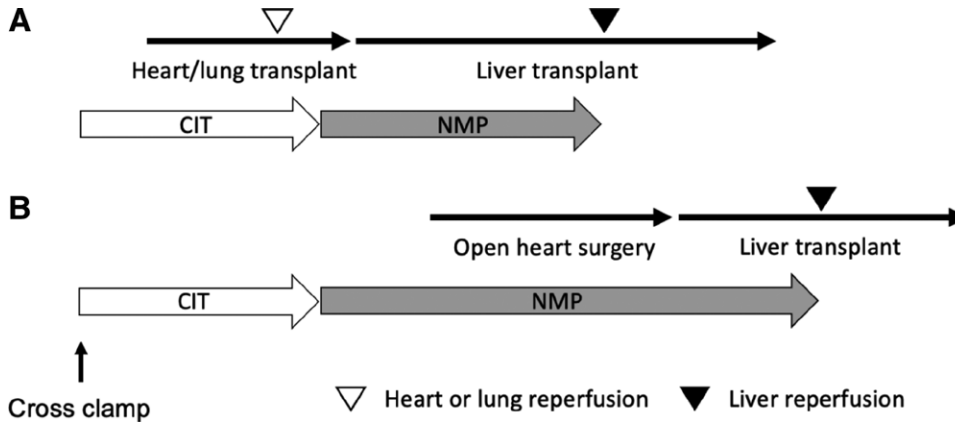

FIGURE 2. Key operative timepoints. Timelines after cross-clamp for combined heart-liver or lung-liver transplant (A) and combined heart surgery and liver transplant (B). Machine perfusion was not used for heart or lung grafts. CIT, cold ischemia time; NMP, normothermic machine perfusion.

developed ischemic cholangiopathy was relisted for retransplantation of the liver a year after his first transplant, but no patient mortality has been observed.

DISCUSSION

Patients with end-stage liver disease are generally deemed ineligible for liver transplantation if they have significant cardiopulmonary diseases. Simultaneous cardiothoracic surgery and liver transplantation present a potential solution, yet many centers hesitate because of the high risks and complexity of such cases.[1,18] Even if patients are listed for liver transplantation with combined cardiothoracic surgery, lengthy waiting times can increase drop-out rates from the transplant list, a situation worsened by the need for standard criteria donors. While using ECDs can expand the donor pool and help expedite transplants, using marginal liver grafts with traditional cold preservation methods raises the risk of morbidity and mortality. In October 2022, our institution implemented NMP as the standard of care, which significantly changed our organ acceptance strategy for high-risk recipients. Thus, this study examines our early experience of NMP in 14 liver transplant recipients who had concomitant cardiopulmonary diseases necessitating combined cardiothoracic surgery, including heart transplants, double-lung transplants, or nontransplant cardiac surgery.

The introduction of liver NMP in our practice allowed our surgical team to accept marginal liver grafts previously deemed unacceptable for combined surgeries. The national organ allocation system gives priority to heart or lung grafts over liver grafts in simultaneous transplants,[19] thus the liver recipients' medical urgency does not aid in prioritizing combined transplant patients. However, since good thoracic organ donors are not always good liver donors, adopting broader liver graft acceptance criteria could improve combined transplant rates. Notably, in our study, 5 of 8 organ donors had significantly high peak liver enzymes (≥300 U/L) and/or total bilirubin levels (≥1.5 mg/dL), with abnormal liver biopsies showing fibrosis or necrosis, conditions once deemed unsuitable for combined transplants with cold preservation. In simultaneous nontransplant heart surgery and liver transplant, the liver graft acceptance criteria were more aggressive. For instance, the donor in case number 11 had liver enzyme levels >5000 U/L, and a liver biopsy revealed confluent necrosis with 10% macrovesicular steatosis. Case number 14 involved a 64-y-old donor with a peak bilirubin of 3.8 mg/dL. Additionally, 8 liver grafts (57%) were retrieved from donors with DRI ≥ 1.4, including 4 lung-liver (100%, median, 1.76) and 4 nontransplant cardiac surgery groups (67%, median, 1.61)—values linked to an increased risk of liver graft failure.[20] This aggressive approach helped decrease wait times for our cohort. In fact, 6 patients were transplanted within 10 d of listing, and all were transplanted within 3 mo of listing, excluding 3 patients listed before NMP implementation.

Our institution has reported outcomes of simultaneous nontransplant heart surgery and liver transplantation using conventional static cold storage.[3,17] In our latest report, patient survival rates were 74.2% after 1 y and 55% after 5 y, which despite being deemed acceptable, are still inferior to the survival rates of benchmark isolated liver transplant.[18,21] Data from the United Network for Organ Sharing show that survival rates for combined liver transplantation and heart surgery are not risk-adjusted, making thorough risk evaluation by each medical center crucial through selective donor and recipient matching. With NMP reducing EAD risk, its regular use could improve outcomes in combined surgeries. In our study, only 2 patients had EAD, and all patients had functional liver grafts postoperation, but the high potential for serious complications is notable. Despite NMP use, all patients undergoing heart surgery faced cardiopulmonary or transplant-related issues, with 4 experiencing significant complications of Clavien-Dindo grade ≥IIIb. It should, however, be noted, that a number of donors was used with NMP that were otherwise not primarily considered because of various risk factors (ie, elevated DRI, time constraints for open offers accepted after cross-clamp, and biopsy results). Further experience is warranted to determine the role of marginal donors with NMP for recipients with higher risk profiles.

It can be argued whether an en bloc approach—where the organs are transplanted simultaneously—is preferable to a sequential approach in combined transplantation. The en bloc approach is in fact associated with a shorter liver CIT, compared with the sequential approach. In combined heart and liver transplantation, both approaches hold similar outcomes, although patients undergoing heart transplants

first potentially fail to proceed to liver transplant surgery because of hemodynamic instability after cardiac grafting.[22] Furthermore, patients who do go through both heart and liver transplantation, sequentially, are at a high risk of developing PRS upon portal vein unclamping because of vulnerability to hemodynamic changes with new cardiac grafts.[1] NMP is, however, known to lower the PRS-risk despite prolonged preservation, giving the surgical teams more flexibility. Still, 2 of 4 heart-liver recipients in this study developed PRS after liver graft reperfusion, indicating the need for more data to fully assess the pros and cons of en bloc versus sequential approach in context of NMP.

NMP has emerged as a critical advancement in the field of liver transplantation, particularly in expanding the donor pool using ECDs, which were previously discarded or underutilized for high-risk recipients.[23,24] Studies have revealed that NMP can increase the use of ECDs and reduce EAD associated with such livers.[25,26] By offering a dynamic, controlled setting for liver assessment and reconditioning pretransplant, NMP is expected to transform the field.[23,27] High-risk recipients, like our study cohort, could benefit from the advantages of NMP.

NMP aids in maintaining hemodynamic stability during liver graft reperfusion, crucial in high-risk cardiopulmonary cases vulnerable to hemodynamic shifts.[28,29] In our cohort, 11 patients (79%) maintained stable systemic hemodynamics after liver graft reperfusion, which we believe is crucial in preventing major intraoperative and posttransplant complications. However, 3 patients (21%) developed PRS, including 2 heart-liver recipients and 1 recipient with heart surgery. Notably, heart-liver recipients experienced a temporary blood pressure drop but maintained mean pressures >60 mmHg. Despite the low volume, our case series shows the beneficial effect of NMP on avoiding serious cardiopulmonary compromise as there were no occurrences of early graft loss or patient mortality.

Figure 2 illustrates the surgical timeline, spanning from the cross-clamp to the conclusion of the procedures. In heart or lung transplantation followed by liver transplantation, since machine perfusion was not used for heart or lung grafts, the cardiothoracic team started a transplant procedure before liver grafts were connected to NMP to minimize heart or lung graft ischemia time. In contrast, in heart surgery followed by liver transplantation, NMP was initiated before a cardiac team started the operation. This sequence of events prevents aborting cardiac surgery if a marginal liver graft fails to meet the acceptance criteria on NMP. In addition to lowering the risk of PRS, this strategy potentially adds another layer of safety when using ECD liver grafts, although no livers were discarded because of viability assessment in combined surgery during the study period.

This report has limitations, including its nature as a single-center retrospective study with a small sample size, and a relatively short follow-up. The evolving role of NMP in clinical transplantation, particularly in combined surgeries, lacks large-scale prospective study validation, thus limiting the generalizability of our approach. More experience from various centers is needed to confirm NMPs effectiveness in improving outcomes. Additionally, the study's short observation period (6–16 mo posttransplant) necessitates further follow-up to assess long-term effectiveness.

In conclusion, our case series shows how NMP can become an effective strategy to enhance outcomes of liver transplant recipients with serious cardiopulmonary diseases. NMP can facilitate the use of liver grafts from ECDs, ensure the organs' viability and easing logistics. By widening graft acceptance criteria and possibly reducing surgical instability risks, NMP could eventually shorten waiting times and improve outcomes. Therefore, NMP could prove valuable for patients requiring simultaneous cardiothoracic surgery and liver transplantation and might help expand the indication.

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