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Back Bench Time: The Hidden Factor of Ischemia in Liver Transplantation

Alexzandria Karina Khan, Mihnea Ioan Ionescu*

Miami Transplant Institute, Jackson Health System, Miami, FL, United States

*Corresponding author:
Mihnea Ioan Ionescu, MD
E-mail: mihnea-ioan.ionescu2@nhs.net

Rezumat

„Back Bench Time" – factorul ascuns al ischemiei în transplantul hepatic

Timpul de ischemie reprezintă un determinant bine stabilit al prognosticului post-transplant hepatic. Supravieţuirea pacientului este semnificativ influenţată de prelungirea timpului de ischemie caldă (TIC) şi rece (TIR) al grefonului în cursul transplantului hepatic. Un element care poate contribui la ambele tipuri de ischemie este timpul de preparare pe masa chirurgicală („back bench time" – BBT). Am identificat BBT ca fiind un potenţial factor etiologic semnificativ al complicaţiilor post-transplant. În cadrul acestei lucrări, s-a efectuat o cercetare sistematică a literaturii în principalele baze de date disponibile. Au fost incluse articole care compară grefe conservate prin perfuzie normotermică versus stocare rece statică, cu timpi măsuraţi de ischemie (TIC şi TIR) şi rezultate post-transplant. În total, au fost selectate 18 studii, însă doar două dintre acestea fac referire explicită la BBT. Acest review sistematic arată că BBT este un factor modificabil al ischemiei, posibil influenţat de experienţa chirurgului, şi care necesită investigaţii suplimentare aprofundate pentru a stabili un prag sigur şi impactul său asupra rezultatelor post-transplant, precum disfuncţia precoce a alogrefei (DPA), colangiopatia ischemică (CI) şi supravieţuirea grefei.

Cuvinte cheie: timp de preparare pe masa de operaţie, ischemie caldă, ischemie rece, perfuzie normotermică, stocare rece statică, supravieţuirea grefei, disfuncţie precoce a alogrefei, colangiopatie ischemică, rezultate post-transplant

Abstract

Ischemia time is a well-established determinant of liver transplant outcomes. Patient survival is substantially affected by prolonged warm (WIT) and cold ischemia time (CIT) of the graft during liver transplant. One component that may be a contributing factor to both WIT and CIT is back bench time (BBT). We have identified BBT as a potentially significant underlying cause of post transplant complications. A literature search was performed using the major available databases. Articles comparing grafts using normothermic machine

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perfusion and static cold storage with measured WIT and CIT, and post-transplant outcomes, were included. A total of 18 studies were selected; however, we were only able to identify two studies that refer to BBT. In this systematic review, we conclude BBT is a modifiable factor of ischemia that may be impacted by the surgeon experience and requires more in depth studies to fully understand a safe threshold and its effect on post transplant outcomes such as EAD, IC, and graft survival.

Keywords: back bench time, back table time, warm ischemia time, cold ischemia time, normothermic machine perfusion, static cold storage, graft survival, patient survival, early allograft dysfunction, ischemic cholangiopathy, post transplant outcomes

Introduction

In the United States, in 2023 there was an all time high of 10,125 adult liver transplants, an overall 71% increase within the last decade due to increased use of DCD livers on normothermic machine perfusion (NMP) (1). A major contributor to the success of liver transplantation is the use of machine perfusion devices. These devices are advantageous because they improve organ survival, minimize ischemia damage, and enable real-time evaluation of the graft's function. Specifically, using NMP may be even more efficient at preserving liver grafts by utilizing a solution of oxygenated red blood cells at body temperature to mimic near-normal physiologic metabolism while also maintaining synthetic liver function (2). In comparison to other preservation methods like static cold storage (SCS) and hypothermic machine perfusion (HMP), the aim is to reduce the metabolic activity of the liver graft after procurement and during transportation to the recipient. While the mechanism of how NMP preserves liver grafts is still unknown, it is theorized that NMP preserves endothelial function and replenishes ATP stores (3).

During the process of liver procurement from the donor, there are several focal points where the graft is susceptible to ischemic damage. The focal points can be identified as cold ischemia time (CIT), warm ischemia time (WIT), and back bench time or back table time (BBT). CIT is characterized as the time from cold storage of the graft on ice to just prior to implantation, usually maintained at a temperature of 0 °C to 4 °C (4). Extended CIT exacerbates injury to key graft components, including mitochondria, hepatocytes, nuclear integrity, and the endothelium (5). Mitochondria face the brunt of ischemic injury and are suspected to be the source of increased levels of AST and ALT associated with liver injury (5). Absent blood flow, as seen in CIT, leads to decreased production of eNOS via downregulation of its transcription factor KLF2. Although a decrease in eNOS may be partially counteracted by the increased hypoxia and hypothermia that upregulates HIF-1α, which causes a short term increase in eNOS. It's hypothesized that increased eNOS is correlated with better protection of the endothelium. Additionally, prolonged time on ice causes decreased production of the AQP8 protein which is associated with increased hepatocyte edema and permeability of mitochondrial membranes (5).

BBT contributes to a substantial part of CIT, especially in the context of preparing a liver graft for machine perfusion (6). BBT is defined as the time during which the organ is prepared after procurement and before implantation into the recipient. This preparation typically includes steps such as vessel reconstruction, removal of excess tissue, and flushing the organ with preservation solution, all performed ex-situ on a sterile table or ice bowl (7). In pancreas and kidney transplant, a short BBT is imperative for better post-transplant outcomes such as decreased graft pancreatitis and thrombosis. In contrast, a longer BBT was associated with delayed graft function in kidneys (7,8). It can be inferred that the same would apply to liver transplantation. It’s well known that liver grafts are vulnerable to ischemia, which is associated with increased hepatocyte injury, early allograft dysfunction (EAD), and ischemic cholangiopathy (IC). It is plausible that shortening BBT would decrease total ischemia time, which could help abate post transplant complications. However, the liver is a much larger organ with different metabolic demands than the pancreas and kidneys. There is a need for liver-specific investigations to determine the safe threshold for BBT and identify the effects on graft outcomes seen with prolonged BBT.

WIT is the time when the graft experiences hypoxia in a normothermic condition (9). During liver transplantation, there are two periods of time that can be categorized as WIT. First being the donor WIT, which occurs after cross clamp in donation after brain death (DBD) or cardiopulmonary death in donor after declaration of circulatory death (DCD) and prior to preservation (SCS or NMP). The second is recipient WIT, which occurs after the graft is removed from ice and before anastomoses are completed during implantation (10). In the study conducted by Al-Kurd et al., they demonstrate the benefits of maintaining a recipient WIT of ≤ 30 minutes, including a lower risk of EAD and graft loss at one and five years post liver transplant. Increased WIT is known to be associated with prominent hepatocyte injury, decreased number of Kupffer cells with decreased phagocytic activity in liver transplant (11). To the best of our knowledge, there are currently no systematic reviews or meta-analyses on WIT and CIT in the context of NMP and the effect on liver transplant outcomes.

Back bench time is a pivotal, yet one of the most overlooked factors in liver transplantation as it contributes to warm and cold ischemia time. This review aims to demonstrate how tracking BBT in the setting of NMP and SCS could transform the outcomes of liver transplantation. Through a systematic review we aim to highlight BBT as a modifiable factor influencing ischemia time and post liver transplant outcomes.

Methods

A literature search was performed using PubMed, Cochrane Database of Systematic Review, EMBASE Elsevier, and Scopus. Several search strings were constructed in collaboration with an experienced medical librarian TG for each database seen in Supplementary data 1, this yielded a total of 1,635 articles. The search strategy can be summarized as CIT OR WIT OR EAD OR patient survival or graft survival AND normothermic machine perfusion OR static cold storage. Only articles available in English were retrieved from January, 1, 2001 to May, 21, 2025. De-duplication was performed manually using Zotero, this resulted in 1,213 articles. Afterwards only articles available in full text were screened, which included 595 articles. Next, titles and abstracts were screened to identify relevant studies, leading to 374 articles. All 374 abstracts were read and studies were selected on inclusion and exclusion criteria by the authors AK and MI by consensus, resulting in 18 studies eligible for this review. A PRISMA flow diagram was constructed to show the article selection process (*Fig. 1*) (12). To assess the risk of bias in each study the Newcastle-Ottawa Scale (NOS) for cohort studies was used (13).

Inclusion Criteria

Inclusion criteria were clinical studies, adult orthotopic liver transplant, RCTs, multicenter studies reporting on the use of normothermic machine perfusion only in comparison to static cold storage, including measurements of WIT, CIT, BBT with the outcomes of EAD, graft survival, and patient survival.

Exclusion Criteria

Exclusion criteria were metanalyses, systematic reviews, reviews, case reports, preclinical studies, protocols, other abdominal transplantation and studies only using hypothermic machine perfusion or HOPE, and normothermic regional perfusion.

Results

A systematic literature search generated 1,635 articles, after de-duplication and screening of titles and abstracts, this led to 595 articles; only 374 were available in full text. After reading the 374 abstracts a total of 18 studies were selected. Of the 18 studies selected, there were 8 retrospective studies, 5 randomized control trials, 1 non-randomized pilot study, 2 prospective clinical studies, 1 observational study and 1 translational research study (*Table 1*). The NOS tool was used to asses the risk of bias in each of the 18 studies (*Table 2*). The studies ranged from the lowest at a rating of 6 to the highest at a score of 9. Overall, the quality of the studies was generally high, indicating a lower risk of bias present. The main difference between the studies regarding quality assessment was the lack of matching for either the demographics of donors or recipients and liver transplant outcomes in the comparability component of the NOS tool. The machine most commonly used for NMP amongst the studies was OrganOx metra. Each study included a comparison group of livers on SCS or NMP for preservation and compared values of CIT and WIT. Outcomes post liver transplant were

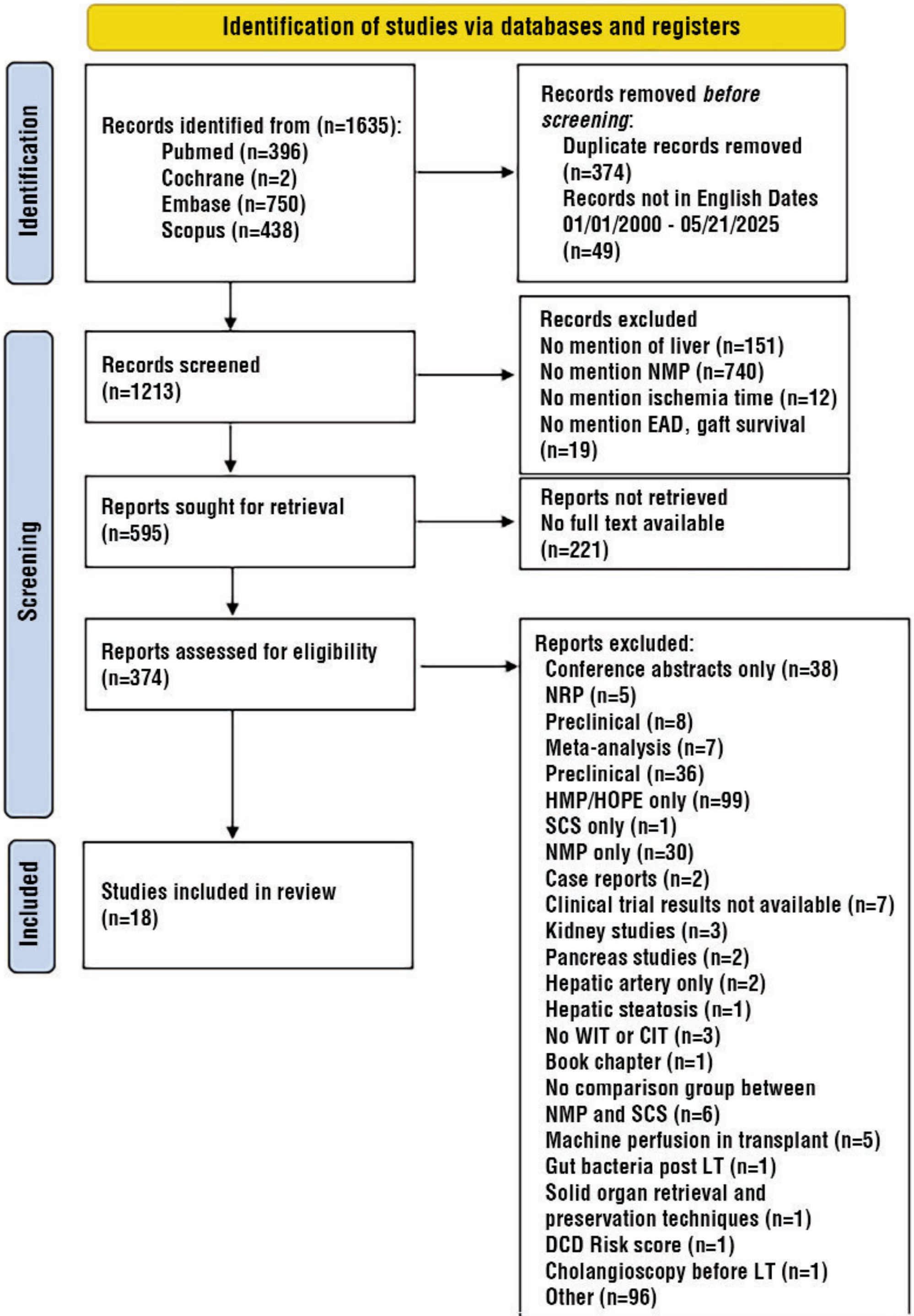

Figure 1. PRISMA Flow diagram for literature search.

observed to identify the role of ischemia time. We found only two studies that were able to describe back bench time.

Functional Warm Ischemia Time

The functional warm ischemia time (fWIT) is a parameter of donor WIT in the context of DCD

Table 1. Summary of findings from each study.

Study	Study type	N		SCS (min)		NMP (min)		SCS	NMP
		SCS	**NMP**	**CIT**	**WIT**	**CIT**	**WIT**	**Post-Transplant Outcomes**	**Post Transplant Outcomes**
Angelico et al 2016	Retrospective clinical study	12	6	456.5	22	91	27	91.7% total reperfusion injury 83.3% total steatosis 2265 mL total blood products after reperfusion 520 mL RBC post operative transfusion	66.7% total reperfusion injury 83.3% total steatosis 1070 mL total blood products after reperfusion 0 mL RBC post operative transfusion
Hoyer et al 2016	Prospective clinical pilot study	106	6	410	26.7	508	26.5	35.9% EAD 2.8% PNF ICU stay 3 days Hospital stay 19 days	0% EAD 0% PNF ICU stay 3 days Hospital stay 21.5 days
Nasralla et al 2018	Randomized control trial	101	121	N/A	16	126	21	0% PNF 33% Post reperfusion injury 29.9% EAD Length of hospital stay 15 days Length of ICU stay 4 days Graft survival at 1 year 0.960 Patient survival at 1 year 0.970	0.8% PNF 12.4% Post reperfusion injury 10.1% EAD Length of hospital stay 15 days Length of ICU stay 4 days Graft survival at 1 year 0.950 Patient survival at 1 year 0.958
Bral et al 2019	Non-randomized pilot study	26 back to base	17	360	20	192	21	0% PNF 19% EAD 0% IC 19% arterial stenosis ICU stay 2 days Hospital stay 16 days Graft survival at 6 mo 100% Patient survival at 6 mo 94%	0% PNF 35% EAD 0% IC 6% arterial stenosis ICU stay 6 days Hospital stay 43 days Graft survival at 6 mo 88% Patient survival at 6 mo 93%
Ghinolfi et al 2019	Open pilot single center randomized prospective trial	10	10	394	69	280	74	10 Patient death 0 PNF 0 Graft loss 10% EAD 10% Post reperfusion syndrome 0 Biliary complications Hospital stay 12 days	0 Patient death 0 PNF 10 Graft loss 20% EAD 30% Post reperfusion syndrome 10 Biliary complications Hospital stay 17 days
Fodor et al 2021	propensity score-matched observational study	59	59	420	42 Anasto-mosis time	360	50 Anasto-mosis time	Patient survival 1 year 82% Graft survival at 1 year 79% 34% EAD Vascular complications 15% Ischemic type bile duct lesions 14%	Patient survival 1 year 81% Graft survival at 1 year 81% 32% EAD Vascular complications 14% Ischemic type bile duct lesions 3%
Markmann et al 2022	Multi-center randomized clinical trial	142	151	338.8	338.8	175.4	454.9	Cross clamp time(out of body time) 9.9% ischemic biliary complications at 12 months 11.6% anastomotic complications Ischemia reperfusion injury 13%	2.6% ischemic biliary complications at 12 months 11.1% anastomotic complications Ischemia reperfusion injury 6%
Gaurav et al 2022	Single center retrospective study	97	67	430	26	396	26	3 year transplant survival 76% 3 year patient survival 88% Re-transplantation 18% Transplant failure at 6 months 13% Hospital stay 18 days Overall biliary complications 42%	3 year transplant survival 76% 3 year patient survival 88% Re-transplantation 12% Transplant failure at 6 months 10% Hospital stay 19 days Overall biliary complications 37%
Minor et al 2022	Randomized controlled study	20	20	454	27.1	485	29.5	30% EAD ICU days 16.6 Hospital stay 38.8 days 3 month graft survival 95% Re-transplantation 5%	20% EAD ICU days 14.3 Hospital stay 30.3 days 3 month graft survival 100% Re-transplantation 0%
Gao et al 2023	Single center retrospective observational study	149	144	355	41	141	36	30 day graft survival 96.6% 90 day patient survival 98% 21.5% EAD ICU stay 5 days Hospitalization 13 days IC 0	30 day graft survival 99.3% 90 day patient survival 98.6% 14.6% EAD ICU stay 3 days Hospitalization 11 days IC 1.8%
Gilbo et al 2023	Multi-center randomized clinical trial	23	42	345	24	124.8	23	Post reperfusion syndrome 34.78% 1 year patient survival 91.3% 1 year graft survival 91.3% Graft loss at 1 year 8.7%	Post reperfusion syndrome 14.29% 1 year patient survival 95.1% 1 year graft survival 90.5% Graft loss at 1 year 9.5%
Yamamoto et al 2023	Single center retrospective study	20	52	333	21.8	155	22.7	PNF 0% Reperfusion syndrome 78.9% EAD 65% IC 20% Graft loss in 5 years 10% Patient death in 5 years 15%	PNF 0% Reperfusion syndrome 16% EAD 25% IC 1.9% Graft loss in 5 years 3.8% Patient death in 5 years 9.6%

Table 1. Cont'd

Study	Study type	N		SCS (min)		NMP (min)		SCS	NMP
		SCS	NMP	CIT	WIT	CIT	WIT	Post-Transplant Outcomes	Post Transplant Outcomes
Werhle et al 2024	Retrospective cohort analysis	74	37	330	23	390	20	90 day Graft loss 1.4% 90 day Mortality 1.4% Any biliary complications15.7% ICU stay days 3 Hospital stay days 14	90 day Graft loss 2.7% 90 day Mortality 2.7% Any biliary complications 16.2% ICU stay days 2 Hospital stay days 11
Vogt et al 2024	Translational research study	6	31	546	50	432	40	50% EAD	35.5% EAD
Stoker et al 2025	Single center retrospective cohort	123	103	378.5	22.8	208.8	22.2	IRI 8% Post-reperfusion syndrome 42.3%	IRI 2.9% Post-reperfusion syndrome 10.7%
Krendl et al 2025	Retrospective observational cohort study	158	174	468	21.5	378	23	2.5% PNF 36.1% EAD 8.2% Rejection within 1 year 36.7% Biliary complications within a year 7.6% Arterial complication within 1 year ICU stay 4 days Hospital stay 19 days	0% PNF 29.9% EAD 4% Rejection within 1 year 42% Biliary complications within a year 8% Arterial complication within 1 year ICU stay 5 days Hospital stay 21 days
Lee et al 2025	Prospective cohort study	254 typical cross clamp	130 prolonged cross clamp	CC=894 DHT47.4	51.2	CC=990 DHT 54.4	49.4	0% PNF 37.6% EAD 22.4% Return to the OR in 90 days 22.3% AKI 2.4% IC	0% PNF 51.2% EAD 23.1% Return to the OR in 90 days 32.2% AKI 3.1% IC
Puttappa et al 2025	Single center retrospective study	59	78	438	12	401	12	37% Postreperfusion syndrome 3% PNF ICU stay 2 days Hospital stay 16 days	15% Postreperfusion syndrome 1% PNF ICU stay 3 days Hospital stay 19 days

Table 2. Quality of studies based on the Newcastle-Ottawa Assessment Scale for Cohort Studies.

Study		Selection				Comparability	Outcome			Total
		1	2	3	4	5	6	7	8	
Angelico et al 2016	Retrospective clinical study	*	*	*	*		*	*		6
Vogt et al 2024	Translational research study	*	*	*	*		*	*		6
Stoker et al 2025	Single center retrospective cohort	*	*	*	*		*	*		6
Ghinolfi et al 2019	Non-randomized pilot study	*	*	*	*		*	*	*	7
Gaurav et al 2022	Single center retrospective study	*	*	*	*		*	*	*	7
Minor et al 2022	Randomized controlled study	*	*	*	*		*	*	*	7
Yamamoto et al 2023	Single center retrospective study	*	*	*	*		*	*	*	7
Lee et al 2025	Prospective cohort study	*	*	*	*		*	*	*	7
Hoyer et al 2016	Prospective clinical pilot study	*	*	*	*	*	*	*	*	8
Bral et al 2019	Randomized control trial	*	*	*	*	*	*	*	*	8
Gilbo et al 2023	Multi-center randomized clinical trial	*	*	*	*	*	*	*	*	8
Nasralla et al 2018	Non-randomized pilot study	*	*	*	*	**	*	*	*	9
Fodor et al 2021	Open pilot single center randomized prospective trial	*	*	*	*	**	*	*	*	9
Markmann et al 2022	propensity score-multicenter matched clinical study	*	*	*	*	**	*	*	*	9
Gao et al 2023	Single center retrospective observational study	*	*	*	*	**	*	*	*	9
Werhle et al 2024	Retrospective cohort analysis	*	*	*	*	**	*	*	*	9
Krendl et al 2025	Retrospective observational cohort study	*	*	*	*	**	*	*	*	9
Puttappa et al 2025	Single center retrospective study	*	*	*	*	**	*	*	*	9

donors, typically it refers to the time elapsed after the withdrawal of life-support when the donor reaches a systolic blood pressure < 50 mmHg or oxygen saturation of < 80% until in situ aortic cold flush occurs (14). The systolic blood pressure and oxygen saturation specifications differ depending on the transplant center. The studies from Angelico et al., Nasralla et al., Bral et al., Wehrle et al., Krendl et al., and Puttappa et al. all used a similar definition to describe their fWIT (14-19). Angelico et al. showed significantly shorter CIT in NMP vs. SCS (91 vs. 456 min; p=0.001), with no difference in fWIT (14). Despite similar steatosis rates (83.3% both groups), NMP livers had lower reperfusion injury than SCS (66.7% vs 91.7%). The prolonged CIT in SCS correlated with greater ischemic damage, reflected in higher blood product use and reperfusion injury. Nasralla et al. reported longer fWIT in NMP vs. SCS (21 vs. 16 min; p = 0.003), yet NMP livers had lower EAD and post-reperfusion syndrome rates (p = 0.0002), demonstrating its ability to mitigate ischemic injury despite extended preservation (15). Bral et al. found similar fWIT between groups (p > 0.99) but lower CIT in local NMP vs. "back-to-base" livers (192 vs. 360 min; p = 0.001) (16). Despite a 3-hour CIT increase due to transport, back-to-base NMP livers outperformed local NMP, highlighting NMP's role in safely extending CIT. ICU stays were longer for local NMP (6 vs. 2 days; p=0.004), likely reflecting selective use in higher-risk grafts. Wehrle et al. found comparable fWIT in NMP and SCS (20 vs 23 min; p = 0.015) but shorter CIT in SCS (390 vs. 330 min; p = 0.015) (16). Despite this, NMP livers had shorter ICU stays (2 vs 3 days; p=0.028), suggesting improved early recovery (17). Krendl et al. reported similar fWIT in NMP and SCS (23 vs 21.5 min; p = 0.807) but significantly shorter CIT in NMP (378 vs 468 min; p ≤ 0.001) (18). Paradoxically, NMP was associated with longer ICU stays (3 vs 2 days; p = 0.028) and higher rates of graft loss, mortality, and biliary complications, despite lower rates of PNF, EAD, and 1-year rejection (17). Puttappa et al. observed identical fWIT (12 min; p ≤ 0.001) and significantly reduced CIT in NMP (401 vs 438 min; p = 0.007) (19). NMP livers lower postreperfusion syndrome (15% vs. 37%; p ≤ 0.001) and reduced PNF rates.

Total Warm Ischemia Time

The total warm ischemia time (tWIT) has a more uniform definition, where studies identify this phase as time from withdrawal of life-sustaining treatment to aortic cold flush (20). The following studies also identified tWIT similarly: Gaurav et al., Gilbo et al., Yamamoto et al., and Stoker et al. (20-23). The study by Gaurav et al. reported identical tWIT in NMP and SCS (26MIN; p = 0.186) but significantly shorter CIT in NMP (396 vs. 430 min; p ≤ 0.001) (20). NMP showed superior short-term outcomes lower EAD, biliary complications, and 10-month graft failure, though 3-year survival was comparable and hospital stays were shorter with SCS. Gilbo et al. found similar tWIT in NMP and SCS (23 vs 24 min; p = 0.89) but markedly reduced CIT in NMP (124.8 vs 345 min; p ≤ 0.001) (21). Despite increased graft loss, NMP correlated with lower post-reperfusion syndrome and higher 1-year patient survival. Yamamoto et al. observed comparable tWIT in NMP and SCS (22.7 vs 21.8 min; p = 0.35) and significantly shorter CIT in NMP (155 vs 333 min; p < 0.01) (22). The NMP group demonstrated reduced reperfusion injury, EAD, ICU stays, and improved 5-year graft and patient survival. Stoker et al. confirmed consistent tWIT in NMP and SCS (22.2 vs SCS 22.8 min; p = 0.576) and shorter CIT in NMP (208.8 vs 378.5 min; p ≤ 0.001), with lower rates of ischemia-reperfusion injury and post-reperfusion injury (23).

Back Bench Time

According to Markmann et al., the cross clamp time was significantly longer in NMP (454.9 vs 338.8 min; p ≤ 0.001), and CIT was significantly reduced in NMP (175.4 vs 338.8 min; p ≤ 0.001) (24). Cross clamp in the Markmann et al. study was defined as the time after hepatectomy, but before implantation. NMP livers had a significant decrease in ischemic biliary complications at 12 months, lower IRI, and lower anastomotic complications than the SCS livers. The cross-clamp time or out-of-body time was significantly longer in the NMP group compared to SCS. This difference likely reflects the additional time required for backbench preparation (BBT), including graft cannulation and setup for machine perfusion - these steps are unique to NMP and would extend ischemia time. The cross clamp time in Lee at al. was defined from aortic cross clamp placement to the start of reperfusion on NMP. This time frame includes both donor hepatectomy time and BBT. In Lee et al., prolonged cross-clamping to on-pump had a significantly longer donor hepatectomy time when compared to typical cross-clamping time (54.4 vs 47.4 min; p = 0.002), and total WIT was shorter in the prolonged cross-clamping time (49.4 vs 51.2 min; p = 0.69) (25). The prolonged cross-clamp time was associated with increased rates of early allograft dysfunction (EAD), return to the OR in 90 days, acute kidney injury (AKI), and IC in NMP livers. Notably, these differences persisted even after adjusting for donor hepatectomy time, which suggests that factors like BBT contributed to the adverse outcomes.

Anastomosis Time

Fodor et al. and Gao et al. recorded their WIT as anastomosis time during graft implantation (26-27). Fodor et al. findings showed WIT was significantly longer in NMP (50 vs 42 min; $p \leq 0.001$) and CIT were nearly the same in NMP and SCS (360 vs 420 min; $p = 0.055$) (26). Lower rates of EAD, vascular complications and ischemic type bile duct lesions were present in the NMP group. Whereas SCS had a higher patient survival at 1 year but lower graft survival at 1 year. Gao et al. was the only study to have significantly shorter WIT (36 vs 41 min; $p \leq 0.001$) and lower CIT in NMP (141 vs 355 min; $p \leq 0.001$) (27). These reductions correlated with lower EAD, shorter ICU and hospital stay, and a higher rate of 30 day graft and 90 day patient survival.

Warm Ischemia Time

The following studies reported WIT but did not specify the measurement time points: Hoyer et al., Ghinolfi et al., Minor et al., and Vogt et al. Hoyer et al. (28-31). reported nearly identical WIT in NMP and SCS (26.5 vs 26.7 min; $p = 0.33$) but longer CIT in NMP (508 vs 410 min; $p = 0.07$) (28). Despite higher CIT, NMP showed lower rates of EAD and PNF. ICU stays were comparable, though hospital stays were extended with NMP. Ghinolfi et al. found similar WIT in NMP and SCS (74 vs 69 min; $p = 0.212$) but significantly shorter CIT in NMP (280 vs 39 min; $p = 0.0001$) (29). NMP was associated only with reduced patient mortality; PNF rates were equal, while SCS showed better outcomes in graft loss, EAD, post-reperfusion syndrome, biliary complications, and hospital stay. Minor et al. demonstrated comparable WIT in NMP and SCS (29.5 vs 27.1 min; no p-value) and CIT (485 vs 454 min; no p-value) (30). NMP outperformed SCS in EAD reduction, shorter ICU and hospital stays, lower re-transplantation rates, and improved 3-month graft survival. Vogt et al. observed similar WIT (NMP 40 vs. SCS 50 min; $p = 0.1864$) but significantly reduced CIT in NMP (432 vs. 546 min; $p = 0.0091$). NMP correlated with lower EAD rates (35.5% vs. 50%) (31). The heterogenous measurement of WIT in these studies may explain the variability of their outcomes.

Discussion

Liver transplantation involves multiple phases where the graft is susceptible to injury. Depending on whether the donor was DCD or DBD, there is a variable amount of time for donor WIT for DCD livers. The donor WIT(dWIT) is defined as the time from withdrawal of life support treatment or cross clamp time to cold perfusion (9). Although the definition of dWIT varies between studies, there has been a call for standardization of the term dWIT (32). The dWIT in DCD is heavily impacted by the length time waiting for cardiopulmonary death to occur, which usually occurs within one to two hours to maintain the quality of the graft (33). The impact of ischemia time on graft viability is profoundly influenced by donor-related factors. As demonstrated in a meta-analysis by den Dekker et al. 2025 (34), they identified CIT as not only a challenge in liver transplantation, but also as a donor-related risk factor that impacts the decision to transplant a liver during NMP.

Hepatectomy Time

The donor hepatectomy time refers to the length of time to extract the liver from the donor body (35). Because this refers to when the graft is not receiving blood at body temperature, it is considered a component of WIT, and longer hepatectomy times are known to impair liver transplant outcomes. In the study conducted by (35), the effect of the donor hepatectomy time on death-censored graft survival and patient survival was comparable to prolonged CIT. The WIT during hepatectomy presents a potential deleterious effect on the graft, as the liver is still in a normothermic environment, and it will maintain a higher rate of metabolism while experiencing ischemia. This allows harmful byproducts to accumulate, such as lactate, reactive oxygen species from oxidative stress, increased cell death, and activation of the innate and adaptive immune response (36). According to Farid et al. (37) a hepatectomy time > 60 minutes is associated with increased graft loss, PNF, and poorer long-term graft survival. This further demonstrates that even during the early process of liver procurement, the WIT as a part of hepatectomy time is critical for the outcome of liver transplants with both short- and long-term consequences.

Back Bench Time

The back-bench time (BBT) represents a unique phase of ischemia that can be classified as either warm ischemia time (WIT) or cold ischemia time (CIT). We identified two studies that also highlight its relevance in liver transplantation. In the Markmann et al. study (24), despite longer cross-clamp time in the NMP livers - likely due to extended back-bench time (BBT) - the use of machine perfusion mitigated adverse outcomes. This was evidenced by lower rates of ischemic biliary complications at 12 months (2.6% vs. 9.9% in SCS), comparable anastomotic complications (11.1% vs. 11.6%), and reduced IRI (6% vs. 13%).

In the Lee at al. study (25), the cross-clamp time described here encompasses the ischemia time from the start of hepatectomy time to the end of BBT in Figure 2. The time for both typical and prolonged cross clamp were adjusted for donor hepatectomy time, the only component of ischemia time that would explain the significant difference between the two groups would be BBT. The prolonged BBT group had significantly higher rates of EAD and AKI. This suggests that prolonged BBT, is a critical yet often unmeasured component of ischemia time, that substantially contributes to liver transplant outcomes. According to the United Network for Organ Sharing there is no recording of BBT. The absence of data further highlights the need for research on BBT.

As illustrated in *Fig. 2*, BBT occurs at two critical time points: One post-hepatectomy, when the liver is prepared and cannulated for NMP. The second is pre-implantation, after NMP or SCS, when the graft is readied for anastomosis. The duration of BBT depends heavily on surgical experience, and prolonged BBT can exacerbate ischemic injury. In the context of NMP, extended BBT prior to perfusion may introduce damage that NMP cannot fully reverse. Conversely, prolonged BBT after NMP - whether on ice or the back table - could negate the benefits of machine perfusion, as the graft is re-exposed to ischemic stress. This was observed in Bral et al. (38), they recorded a CIT for complete back table preparation for a median of 2 hours and 47 minutes, compared to a median of 11.5 hours on NMP, they still considered BBT as significant enough to impede the benefits of NMP (38). There is a plethora of articles that describe livers on NMP, however we were only able to identify 2 studies that demonstrate this phenomenon. It can be inferred that during the BBT the liver is subject to re-warming and therefore increased metabolic activity - which means BBT possibly contributes to both cold and warm ischemia time. Exploring BBT as an independent factor in liver transplant outcomes may offer valuable insight especially in the context of NMP.

In the back to base model, there is an associated prolonged CIT as the graft is transported from the donor hospital (*Fig. 3*) to the recipient hospital where NMP is initiated (16). The severity of the CIT injury is dependent on the travel time and distance between the donor and recipient hospital. With the prolonged CIT in back to base, even though the liver is eventually put on NMP, it may not be sufficient to negate the ischemic damage from CIT.

Preservation Time

In liver transplantation, grafts can either be preserved on ice as SCS or more recently on a machine such as NMP. While SCS has been the mainstay for liver preservation for a long time and known for its ability to decrease the metabolism of the graft, NMP is arguably more efficient at preservation by providing a near physiologic environment for the graft at 37°C with oxygenated blood flow (15). NMP proves to be more advantageous than SCS, with its ability to extend preservation time, reduce IRI, perform real time viability assessments, and allows greater use of extended-criteria donors (2,38). NMP can safely preserve a graft up to 22.5 hours (38), whereas with SCS a liver can be preserved for 8 to 12 hours before graft function and patient survival is compromised (39). While NMP has emerged as a promising alternative to SCS for graft preservation, critical questions remain regarding its upper time limits. One randomized control trial suggests that NMP may mitigate IRI in DCD livers, but as highlighted by Archie et al. (40), the maximal safe duration of NMP has yet to be established.

NMP can reverse the effects of IRI at implantation by establishing oxygenated blood flow soon after donor hepatectomy and back bench time. IRI can occur at two places, once before NMP is initiated and after reperfusion is established during implantation (*Fig. 2*) (41).

This ischemic time can be variable based on 2 factors, one being the time it takes for the donor to expire in DCD cases and the second being influenced by the expertise and skill of the surgeon or surgical team performing the operation. It can be inferred that a surgeon with more experience will be able to perform the hepatectomy and back bench procedures much faster than a surgeon with less experience. The length of time it takes to complete these steps can greatly effect the outcomes of the transplant as we discussed earlier.

IRI is described as having 2 phases, first the

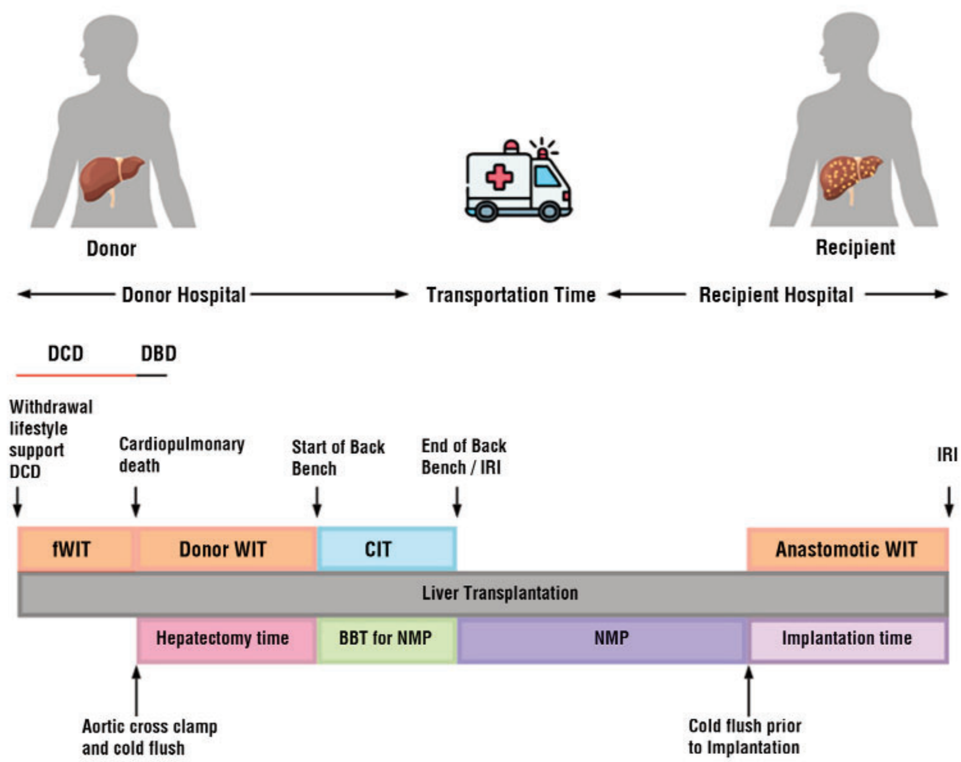

Figure 2. NMP in the donor hospital phases of ischemia time during liver transplantation.

ischemia phase where metabolic demand is not adequately met and the second phase is reperfusion - defined as an inflammatory immune response to ischemia. The two BBT timepoints one prior to the start of NMP and other prior to implantation (*Fig. 2*) can prolong ischemia time, potentially worsening IRI. Since increased IRI is linked to poor graft outcomes (42), the BBT is important to monitor.

Implantation Time

Implantation time is also considered a factor into WIT. Implantation can be briefly described as the interval from IVC anastomosis to reperfusion (43). Specifically, the anastomotic WIT is characterized by the time from when the graft was removed from ice to when blood flow was establish to the graft in the recipient after the release of vascular clamp (20), is known to alter post liver transplant outcomes. This was observed in study Fodor et al. 2021 (26), even though anastomoses time was prolonged in NMP livers it still yielded better outcomes in terms of increased graft survival at one year, lesser EAD, less vascular complications and decreased ischemic bile duct.

Conclusion

After reviewing 18 studies that compared WIT and CIT in the settings of NMP versus SCS, we have observed that longer warm ischemia time is associated with poor liver transplant outcomes, such as the development of EAD, longer ICU and hospital stay, along with shorter graft and patient survival. Since the approval of machine perfusion devices by the US Food and Drug Administration in 2021, NMP has transformed transplant outcomes by mitigating ischemia-reperfusion injury and expanding the donor pool (1). Through the use of technology like NMP the practice of liver transplantation has been altered. NMP has served as a platform for therapeutic innovation in liver transplant, via interventions altering the graft perfusate such as anti-inflammatory drugs, mesenchymal stem cells, gene therapies, and defatting compounds have already been studied (2). Yet amidst these advances, there remains a fundamental gap in the investigation of BBT and its impact on liver transplant outcomes. In this review, we have synthesized evidence that BBT is a major contributing factor to both warm and cold

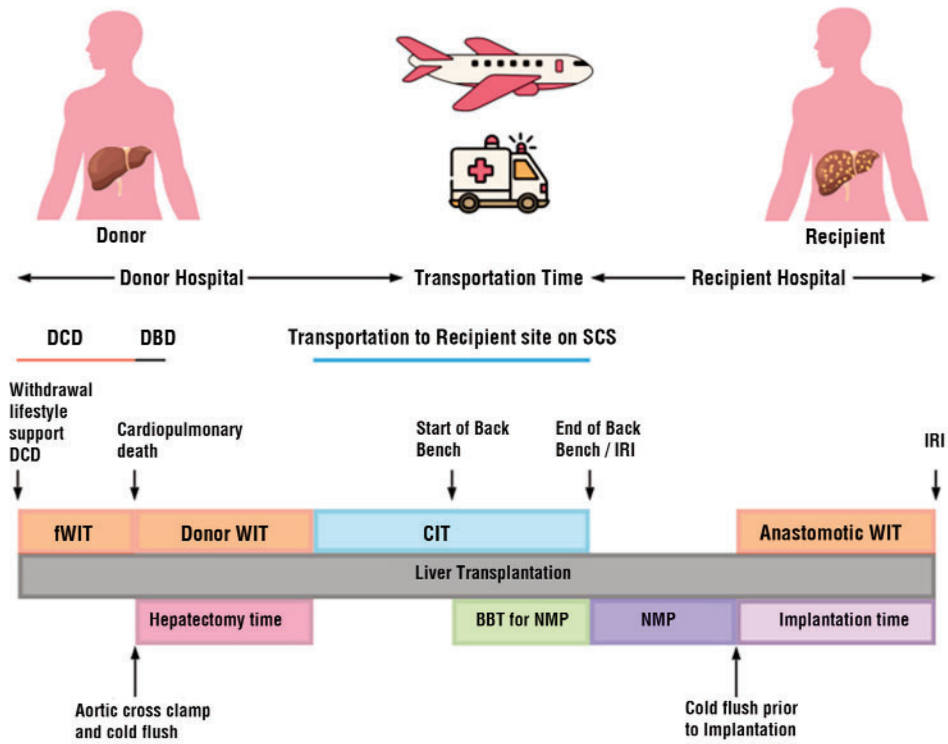

Figure 3. Back to base model with phases of ischemia time during liver transplantation.

ischemia time. While ischemia time is a well known determinant of liver transplant outcomes, the role of back bench time remains a hidden unmeasured variable. Unlike in SCS, the liver during BBT is maintained in a cold environment but still experiences rewarming to a certain extent, at this period the metabolic rate of the graft is elevated thus allowing more ischemic damage to occur. Additionally, the experience of the surgeon performing the BBT can contribute to a longer BBT, which can prolong the ischemia even more. The two phases of BBT, one prior to NMP and implantation, the use of NMP may not be able to mitigate this ischemia, and is a very crucial variable to measure.

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Conflicts of Interests

The authors declare no conflicts of interests.

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Supplementary

Supplemental data 1. Search strategy.

Cochrane N= 2

((((Ischemia OR "cold storage" OR "cold ischemia" OR "warm ischemia" OR "Warm Ischemia" OR "Cold Ischemia" OR "early allograft dysfunction" OR EAD OR "graft survival" OR "patient survival" OR "overall survival") AND (liver OR Liver OR hepatic) AND ("liver transplant" OR "Liver Transplantation" OR graft)) AND ("Machine Perfusion" OR "normothermic machine perfusion" OR NMP OR Transmedics OR OrganOx OR Perfusion/methods) AND ("static cold storage" OR SCS OR "cold storage" OR "Organ Preservation/methods"))) NOT (animals NOT humans) NOT (mice OR rat OR rats OR murine OR canine OR dog OR dogs OR porcine OR pig OR pigs OR rabbit OR rabbits OR "animal model" OR "animal models" OR "animal study")

Pubmed N=396

((((Ischemia OR "cold storage" OR "cold ischemia" OR "warm ischemia" OR "Warm Ischemia"[Mesh] OR "Cold Ischemia"[Mesh] OR "early allograft dysfunction" OR "EAD" OR "graft survival" OR "patient survival" OR "overall survival") AND (liver OR "Liver"[Mesh] OR "hepatic") AND (liver transplant OR "Liver Transplantation"[Mesh] OR "graft")) AND ("Machine Perfusion" OR "normothermic machine perfusion" OR "NMP" OR "Transmedics" OR "OrganOx" OR "Perfusion/methods"[Mesh]) AND ("static cold storage" OR "SCS" OR "cold storage" OR "Organ Preservation/methods"[Mesh]))) NOT ("animals"[Mesh] NOT "humans"[Mesh]) NOT (mice OR rat OR rats OR murine OR canine OR dog OR dogs OR porcine OR pig OR pigs OR rabbit OR rabbits OR "animal model" OR "animal models" OR "animal study")

EMBASE N= 750

((((Ischemia OR ’cold storage’ OR ’cold ischemia’ OR ’warm ischemia’ OR ’Warm Ischemia’ OR ’Cold Ischemia’ OR ’early allograft dysfunction’ OR EAD OR ’graft survival’ OR ’patient survival’ OR ’overall survival’) AND (liver OR Liver OR hepatic) AND (’liver transplant’ OR ’Liver Transplantation’ OR graft)) AND (’Machine Perfusion’ OR ’normothermic machine perfusion’ OR NMP OR Transmedics OR OrganOx OR Perfusion/de) AND (’static cold storage’ OR SCS OR ’cold storage’ OR ’Organ Preservation/methods’))) NOT (animals NOT humans) NOT (mice OR rat OR rats OR murine OR canine OR dog OR dogs OR porcine OR pig OR pigs OR rabbit OR rabbits OR ’animal model’ OR ’animal models’ OR ’animal study’)

Scopus N=438

((((ischemia OR "cold storage" OR "cold ischemia" OR "warm ischemia" OR INDEX ("warm ischemia") OR INDEX ("cold ischemia") OR "early allograft dysfunction" OR ead OR "graft survival" OR "patient survival" OR "overall survival") AND (liver OR INDEX (liver) OR hepatic) AND ("liver transplant" OR INDEX ("liver transplantation") OR graft)) AND ("machine perfusion" OR "normothermic machine perfusion" OR nmp OR transmedics OR organox OR INDEX (perfusion)) AND ("static cold storage" OR scs OR "cold storage" OR INDEX ("organ preservation"))) AND NOT (INDEX (animals) AND NOT INDEX (humans)) AND NOT (mice OR rat OR rats OR murine OR canine OR dog OR dogs OR porcine OR pig OR pigs OR rabbit OR rabbits OR "animal model" OR "animal models" OR "animal study")) AND PUBYEAR > 1999 AND PUBYEAR < 2026 AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (LANGUAGE , "English"))