Current Transplantation Reports (2023) 10:1–11
https://doi.org/10.1007/s40472-023-00388-3

KIDNEY TRANSPLANTATION (ML HENRY AND R PELLETIER, SECTION EDITORS)

Hypothermic Machine Perfusion of Extended Donor Criteria Renal Allografts Before Kidney Transplantation: a Systematic Review

Mahmoudreza Moein[1] · Joseph F. Toth[1] · Jonathan Capelin[1] · Reza Saidi[1]

Accepted: 8 November 2022 / Published online: 24 January 2023

Abstract

Purpose of review Due to the growing need for organs to be transplanted, methods for expanding organ utilization must be explored. While effective in cost and outcomes for optimal donor organs, traditional static cold storage (SCS) is less suitable for use in marginal organ transplants, where hypothermic machine perfusion has several attractive advantages. This systematic review aims to summarize the literature regarding outcomes for transplanting extended criteria donor kidneys preserved by machine perfusion.

Recent findings A systematic literature search of PubMed and the ClinicalTrials.gov registry was performed. eGFR, serum creatinine, delayed graft function rate, length of stay and graft, and patient survival rate were demonstrated. Sixteen articles that assessed kidney function and patient outcomes after using hypothermic machine perfusion as part of organ revitalization were included. Regarding DGF, HMP showed a significantly lower DGF rate compared to SCS ($P < 0.0001$). Two studies found a significantly lower hospital stay in the HMP group. eGFR was comparable between the HMP and SCS groups. One-year allograft survival was meaningfully higher in the HMP group ($P = 0.04$). One-year patient survival was comparable between the two groups.

Summary Our systematic review summarized the literature regarding outcomes for transplant of extended criteria and marginal kidneys preserved by hypothermic machine perfusion and possible comparison with the traditional static cold storage method, with particular emphasis on patients' outcomes. Hypothermic machine perfusion can improve some aspects of the transplant outcomes in extended criteria donor kidneys.

Keywords Kidney transplantation · Hypothermic machine perfusion · Extended criteria donor kidneys · Marginal kidneys · Outcomes

Abbreviations

CIT	Cold ischemia time
DGF	Delayed graft function
ECD	Extended criteria donor
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HMP	Hypothermic machine perfusion
$HMPO_2$	Hypothermic machine perfusion with oxygen
IRI	Ischemic reperfusion injury
KDPI	Kidney risk profile index
KT	Kidney transplantation
LOS	Length of stay
OPTN	Organ procurement and transplantation network
SCD	Standard criteria donor
SCS	Static cold storage
SCR	Serum creatinine

Mahmoudreza Moein and Joseph F. Toth have contributed equally to this work and share the first authorship.

This article is part of the Topical Collection on *Kidney Transplantation*

✉ Reza Saidi
SaidiR@upstate.edu

[1] Department of Surgery, Division of Transplantation, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA

Introduction

Due to the growing need for organs to be transplanted, methods for expanding organ utilization must be explored. One strategy has been increasing the donor pool via increasing donor registrations, promoting living donor transplants, and using extended criteria donors [1, 2]. The second way

to increase the number of organs used is to optimize the donor yield. This means making sure available organs are not wasted, as is the case for approximately 20% of deceased donor kidneys in the USA [3]. One way to accomplish this has been by implementing ex vivo hypothermic machine perfusion before transplantation.

While effective in cost and outcomes for optimal donor organs, there is still some controversy about the overall efficacy and outcomes of the marginal and extended donor criteria kidney transplantation preserved either by the traditional static cold storage (SCS) or the ex vivo hypothermic perfusion machine (HMP). Some studies discussed that the static cold storage method is less suitable for use in marginal and extended donor criteria organ transplants, where hypothermic machine perfusion has some advantages, such as the ability for organ function assessment and possible necessary interventions such as adding medications before transplantation and also reducing some adverse events such as ischemic-reperfusion injury (IRI) [4–7].

This systematic review aims to summarize and assess the literature regarding outcomes for transplant of extended criteria and marginal kidneys preserved by ex vivo hypothermic machine perfusion and possible comparison with the traditional static cold storage method, with particular emphasis on investigating the effect these interventions had on delayed graft function (DGF) and short- and long-term patient and graft survival to due to the controversy surrounding the use of HMP for marginal kidneys.

Methods and Materials

Search Strategy

A systematic literature review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) (Fig. 1). A wide-ranging screening of the National Library of Medicine Database and the Scopus was performed on March 1, 2022, and the last updated on April 3, 2022, in order to identify literature on hypothermic Machine perfusion prior to transplantation in extended donor criteria and marginal kidneys. The following search queries were performed:

1- "Marginal Kidney AND Machine perfusion AND Transplant."
2- "Marginal Kidney AND donor AND Hypothermic machine perfusion AND Transplant."
3- "Extended donor criteria kidney AND Machine perfusion AND Transplant."
4- "Extended donor criteria Kidney AND donor AND Hypothermic machine perfusion AND Transplant."

Additionally, the ClinicalTrials.gov registry of the US National Library of Medicine was searched on March 1, 2022, for the following terms:

"Kidney AND donor AND Machine perfusion AND Transplant"

No clinical trial was identified (Fig. 2).

Inclusion and Exclusion Criteria

Articles meeting inclusion criteria for this review were published in prospective, retrospective, clinical trials, and systematic reviews about hypothermic machine perfusion prior to transplantation in marginal and extended donor criteria kidneys. Letters, case reports, case series, and video articles were excluded. Also, follow-up studies that reported no further information on the postoperative outcomes of the respective recipients were excluded.

Data Extraction

A three-stage independent screening method was applied by two of the authors (JC and MM). In case of discordance, the corresponding author, RS, was consulted, and the consensus was made via discussion. During stage one of data extraction, the titles and abstracts of all retrieved records were reviewed, and unsuitable studies were excluded. During stage two, full-text articles of the remaining studies were read carefully and assessed for inclusion criteria, and studies without clinical trials were excluded.

During stage three, articles without relevant outcomes were excluded. Extracted data were reviewed and analyzed by all the authors.

Statical Analysis

DGF, 1-year allograft, and patient survival rates were assessed using Cochran's Q test, and 95% CIs were calculated for the continuous and dichotomous data and reported as an odds ratio (OR) or risk difference (RD). The overall studies comparison was defined as statistically significant when the P value was < 0.05.

Results

A systematic literature search of the National Library of Medicine database and Scopus identified 3224 records. Based on the title and abstract, 3148 papers were excluded, and 76 articles went for full-text analysis. Of these, 44 were excluded as they did not have a clinical outcome. The remaining 32 articles all assessed the outcome of hypothermic machine perfusion. Finally, 16 articles that assessed kidney function and

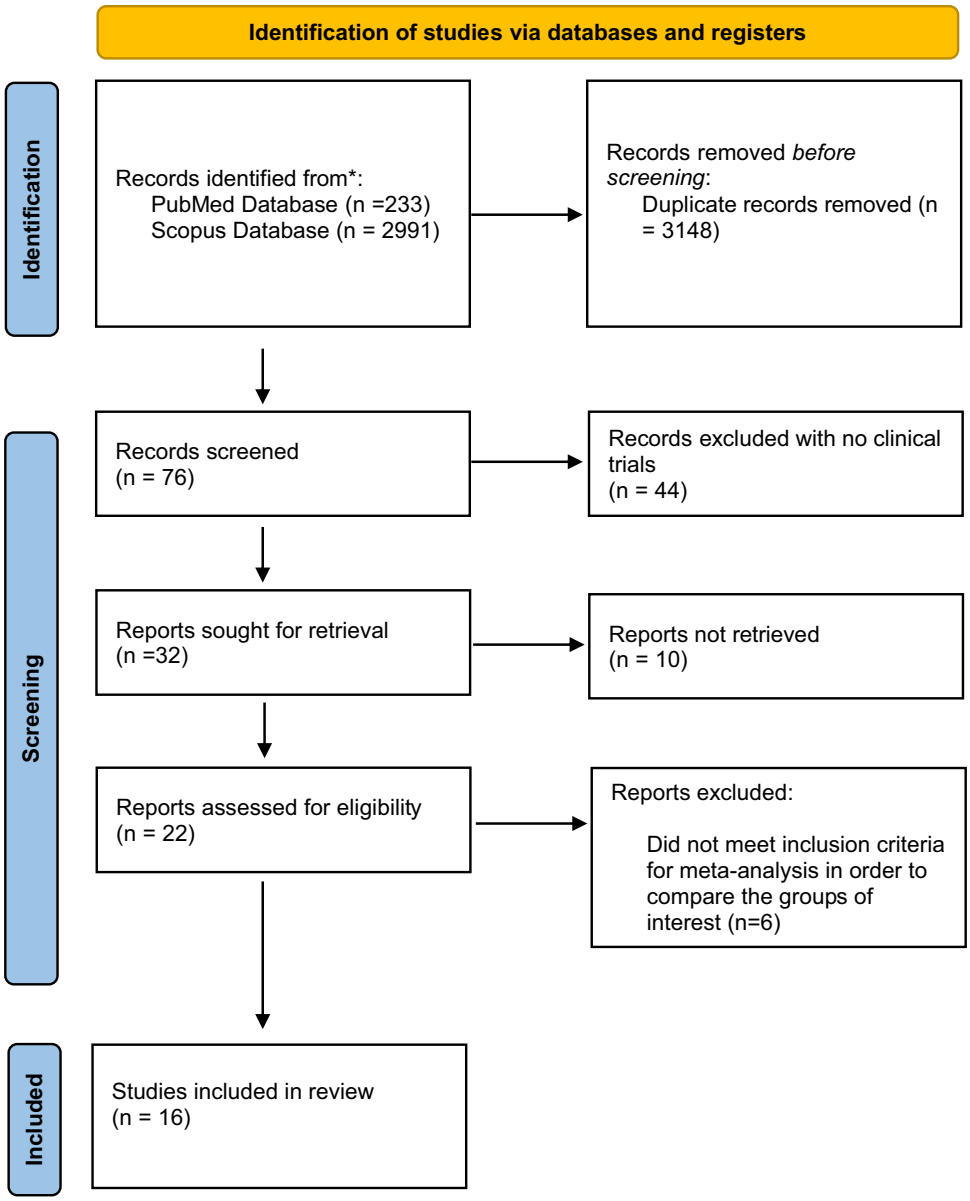

Fig. 1 Flowchart of the performed systematic literature research [8]

patient outcomes after using hypothermic machine perfusion as part of organ revitalization were included in this systematic review based on the inclusion criteria and follow-ups. Table 1 shows the overall number of studies, the number of cases in each study, and the study type. A total of 15 of the 16 articles reported DGF post-transplant as a part of their study (Table 2), and 9 studies reported an acute rejection rate. However, the studies' defined time frame for acute rejection differed (Table 3). Seven studies reported their renal allograft recipients' median length of stay (Table 4). Seven studies followed the post-transplant kidney function by GFR (Table 5), and ten studies used SCr to follow up the kidney function (Table 6); 13 articles followed up on their patients' allograft survival and reported it as the graft survival rate (Table 7). Nine articles reported their patient survival rate (Table 8).

Delayed Graft Function (DGF)

DGF is defined as failure of the renal transplant to function immediately, with the need for dialysis in the first post-transplantation week. Five of fifteen articles that reported the DGF rate found a significant difference when they compared the DGF rate in their SCS group and HMP group, and the DGF rate was higher in the SCS group compared to the HMP group. The remaining ten studies did not see a meaningful difference when they compared the DGF rate between SCS and HMP groups. Figure 1 shows the overall comparison of the DGF rate. The pooled results showed a significantly higher DGF rate in the SCS group compared to the HMP group ($OR = 1.64$, 95% $CI = 1.35–2$, $P < 0.0001$, $P_{\text{heterogeneity}} = 0.30$, $I^2 = 14\%$). Table 2 shows the DGF rate and comparison in different studies.

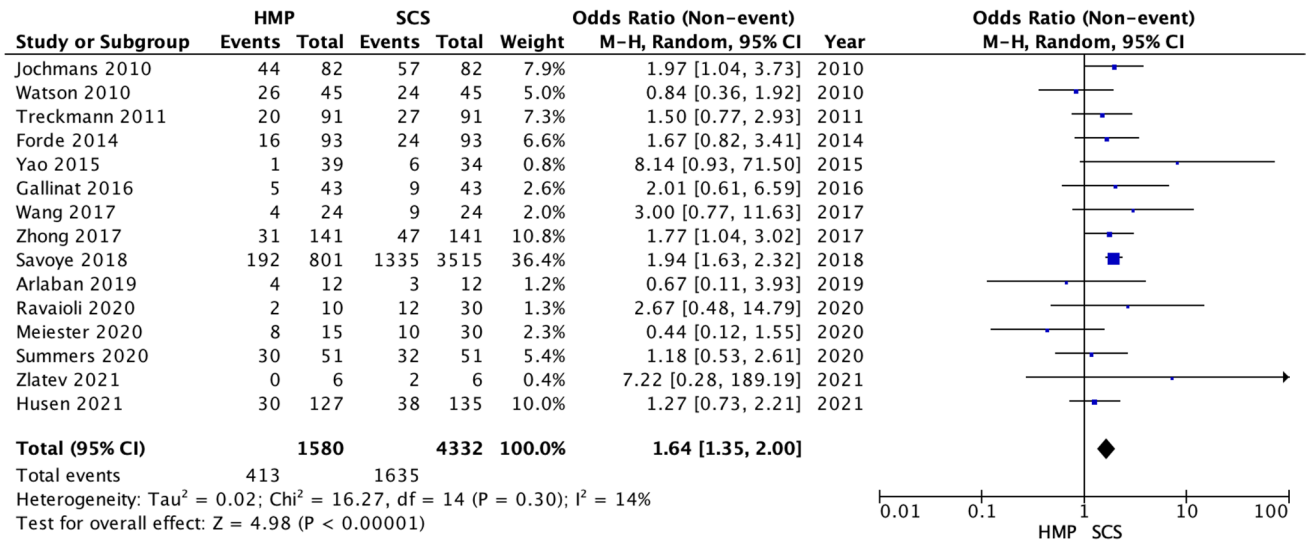

Fig. 2 DGF comparison between the HMP and SCS groups

Table 1 Overall studies meet the inclusion criteria with publication year and the number of cases

Study	Total cases	SCS	HMP	Publication year	Study type
Jochmans et al. [9]	164	82	82	2010	RCT
Watson al. [10]	90	45	45	2010	RCT
Treckmann et al. [11]	182	91	91	2011	Prospective
Forde et al. [12]	186	93	93	2014	Retrospective
Yao et al. [13]	73	34	39	2015	Prospective
Gallinat et al. [14]	86	43	43	2016	Prospective
Wang et al. [15]	48	24	24	2017	RCT
Zhong et al. [16]	282	141	141	2017	Prospective
Savoye et al. [17]	4316	3515	801	2018	Retrospective
Foucher al. [18]	1889	1063	826	2019	Retrospective
Arlaban et al. [19]	24	12	12	2019	Prospective
Ravaioli et al. [20]	40	30	10	2020	CT
Meister et al. [21]	45	30	15	2020	Retrospective
Summers et al. [22]	102	51	51	2020	RCT
Zlatev et al. [23]	12	6	6	2021	Prospective
Husen et al. [24]	262	135	127	2021	RCT

Acute Rejection Rate

Of the nine articles that evaluated the acute rejection post-transplant, one study found a significantly higher acute rejection rate in the HMP group. Watson et al. [10] reported an acute rejection of 22% in the SCS group and 7% in the HMP group ($P=0.06$). On the other hand, Gallinat et al. [14] study found a completely opposite acute rejection rate. They reported a 38.5% acute rejection rate in the HMP group and 10% in the SCS group ($P=0.01$). Table 3 demonstrates the acute rejection rate in different studies.

Length of Stay (LOS)

Only seven studies reported the length of hospital stay for their SCS and HMP group patients. Two studies found a significant difference between the groups. Wang et al. [15] reported a mean of 19.3 days to stay for the SCS group and 12.4 days to stay for the HMP group ($P=0.001$). Savoye et al. [17] reported a mean of 17.1 days to stay for the SCS group and 15.6 days to stay for the HMP group ($P<0.001$). Table 4 shows the length of hospital stay in different studies.

Table 2 Studies assessed the DGF rate comparison between HMP and SCS in the extended donor criteria kidneys

Study	Dgf (%) in SCS	Dgf (%) HMP	*P*-value
Jochmans et al. [9]	69.5	53.7	0.025
Watson et al. [10]	53.3	57.8	0.80
Treckmann et al. [11]	29.7	22	0.27
Forde et al. [12]	25.8	17.2	NS
Yao et al. [13]	17.64	2.56	0.026
Gallinat et al. [14]	20.9	11.6	0.38
Wang et al. [15]	37.5	16.7	0.03
Zhong et al. [16]	33.3	22	0.033
Savoye et al. [17]	38	24	< 0.001
Arlaban et al. [19]	25	33.3	NS
Ravaioli et al. [20]	40	20	0.61
Meister et al. [21]	33	53	0.20
Summers et al. [22]	62.8	58.8	0.69
Zlatev et al. [23]	33	0	0.33
Husen et al. [24]	28.1	23.6	0.40

Table 3 Studies assessed the acute rejection rate comparison between HMP and SCS in the extended donor criteria kidneys

Study	SCS acute rejection rate (%)	HMP acute rejection rate (%)	*P* value
Jochmans et al. [9]	12.2	7.3	0.28
Watson al. [10]	22	7	0.06
Treckmann et al. [11]	17.6	18.7	0.98
Yao et al. [13]	3	7.9	0.36
Gallinat et al. [14]	10	38.5	0.01
Wang et al. [15]	8.3	4.1	0.551
Ravaioli et al. [20]	6.6	10	NS
Summers et al. [22]	19.6	19.6	1
Husen et al. [24]	13.3	18.1	0.29

Table 4 Studies assessed the length of hospital stay comparison between HMP and SCS in the extended donor criteria kidneys

Study	LOS in SCS (mean days)	Los in HMP (mean days)	*P*-value
Jochmans et al. [9]	19	17	0.24
Treckmann et al. [11]		Comparable	NS
Wang et al. [15]	19.4	12.3	0.001
Savoye et al. [17]	17.1	15.6	< 0.001
Ravaioli et al. [20]	24	17	0.09
Meister et al. [21]	21	25	0.57
Summers et al. [22]	10	9	0.23
Zlatev et al.* [23]	17.8 ± 6.6	16.6 ± 5.0	0.924

*Days ± SD

eGFR

Seven of sixteen articles reported post-transplant GFR. The follow-up duration was from 7 days to 1 year. Yao et al. [13] study was the only one that reported a meaningful difference after comparing GFR between the SCS and HMP groups after 6 months. The mean GFR with standard deviation was 100.8 ± 29.5 ml/min/1.73 m2 in the HMP group and 85.2 ± 20.37 ml/min/1.73 m2 in the SCS group ($P = 0.0128$). Meister et al. [21] found a meaningful difference after comparing GFR between the SCS and HMP groups after 7 days, but with the 6-month follow-up, the GFR rate was comparable between the groups. Table 5 shows the follow-up duration and the GFR outcome in different studies.

Serum Creatinine (SCr)

Ten papers had reported the follow-up serum creatinine. The follow-up duration was from the discharge to 1 year. Four studies reported a meaningful difference after comparing SCr between the SCS and HMP groups, and SCr was lower in the HMP group compared to the SCS group. Table 6 summarizes each group's follow-up duration and serum creatinine level.

Graft Survival

Thirteen studies of the overall 16 studies followed the allograft survival, and 3 reported a meaningful difference between the SCS and HMP groups. Treckmann et al. [11] reported graft survival after 1 year of following up, and it was 80.2% in the SCS group and 92.3% in the HMP group ($P = 0.02$). Zhong et al. [16] found a meaningful higher graft survival rate in the HMP group after 1 and 3 years of follow-up. The 1-year graft survival rate was 93% in the SCS group vs. 98% in the HMP group ($P = 0.026$), and the 3-year graft survival rate was 82% in the SCS group vs. 93% in the HMP group ($P = 0.036$). On the other hand, although Meister et al. [21] found a meaningful difference between the SCS and HMP groups' graft survival, the outcome was in favor of the SCS group. After 6 months of follow-up, they reported a 100% graft survival, both deaths censored and uncensored for the SCS group and 93% death censored and 87% non-death censored for the HMP group ($P = 0.04$). Figure 3 shows the overall comparison of the 1-year graft survival rate. The pooled results showed a significant difference in 1-year graft survival rate between the two groups, and the HMP group had a better 1-year graft survival rate ($RD = 1.02$, 95% $CI = 1.00–1.04$, $P = 0.04$, $P_{\text{heterogeneity}} = 0.30$, $I^2 = 15\%$). Table 7 demonstrates the studies with a graft survival assessment.

Table 5 Studies assessed the GFR comparison between HMP and SCS in the extended donor criteria kidneys

Study	Follow up duration	GFR SCS (ml/min/1.73 m2)	GFR HMP ml/min/1.73 m2	*P* value
Watson al. [10]	7 days	14.9	17	0.24
	3 months	48.9	46	0.42
	1 year	46.2	46.6	0.64
Yao et al.* [13]	6 months	85.2 ± 20.37	100.8 ± 29.5	0.0128
Savoye et al. [17]	1 year	42.9	42.5	NS
Meister et al. [21]	7 days	31	14	0.02
	3 months	35	29	0.30
	6 months	38	32	0.28
Summers et al. [22]	7 days	9.3	12.7	0.23
	3 months	33.6	44.8	0.06
	1 year	44.1	46.8	0.20
Zlatev et al.* [23]	3 months	70 ± 13	45 ± 19	0.23
Husen et al. [24]	7 days	26	27.1	0.63
	3 months	39.8	38.1	0.36
	6 months	39.6	38	0.38
	1 year	41.2	39.9	0.53

*Mean ± SD value

Table 6 Studies assessed the serum creatinine comparison between HMP and SCS in the extended donor criteria kidneys

Study	Follow up duration	SCR SCS (mg/dl)	SCR HMP (mg/dl)	*P* value
Jochmans et al. [9]	14 days	5.1	4.1	0.001
	1 month	2.1	1.7	0.017
Forde et al. [12]	1 month	1.84	1.64	0.0096
	6 months	1.75	1.56	0.0236
	1 year	1.59	1.47	0.1630
Yao et al. [13]*	6 months	1.16 ± 0.33	1.03 ± 0.23	0.0637
Gallinat et al. [14]	3 months	1.61	1.58	0.73
	6 months	1.54	1.55	0.69
	1 year	1.44	1.46	0.38
Wang et al. [15]	Discharge	1.61	1.43	0.004
	6 months	1.46	1.18	0.058
Zhong et al. [16]	7 days	2.26	1.92	0.024
Arlaban et al. [19]	1 year	1.3	1.5	0.521
Ravaioli et al. [20]	5 days	4.1	3.5	0.46
Meister et al. [21]	3 months	2.1	2.6	0.25
	6 months	2.1	2.6	0.35
Summers et al. [22]	7 days	6.2	4.84	0.22

*Mean ± SD

Patient Survival

The follow-up duration for patient survival rate varied from 3 months to 5 years between the studies. Among the nine articles that reported their patient survival rate, only 1 study had a statistically significant difference. Husen et al. [24] followed their cases for 1 year, and the patient survival rate was 98.5% in the SCS group and 92.9% in the HMP group ($P = 0.03$). Figure 4 shows the overall comparison of the 1-year patient survival rate. The pooled results showed no significant difference in the 1-year patient survival rate between the two groups ($RD = 0.98$, 95% $CI = 0.95–1.01$, $P = 0.14$, $P_{\text{heterogeneity}} = 0.31$, $I^2 = 16\%$). Patient survival outcomes are summarized in Table 8.

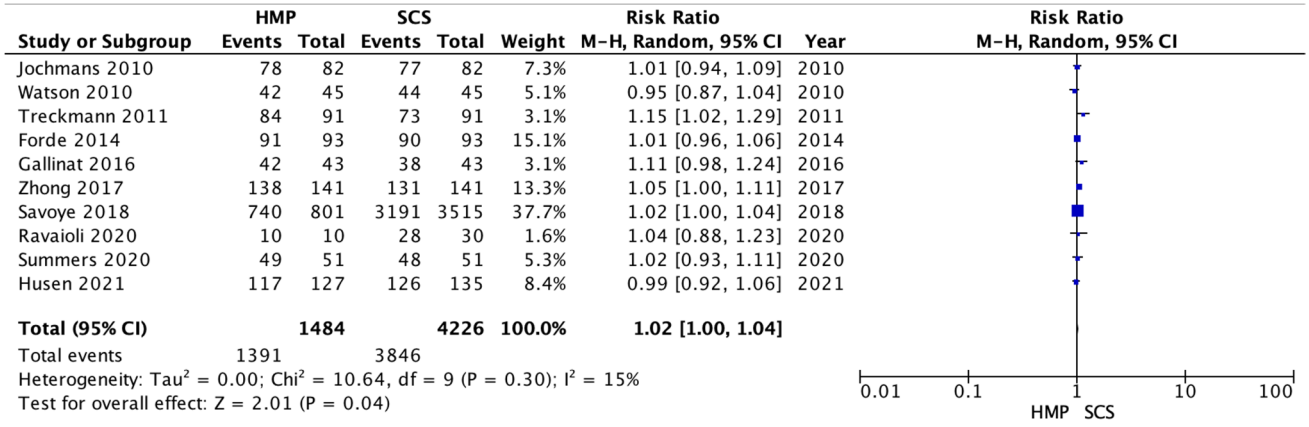

Fig. 3 1-year graft survival comparison between the HMP and SCS groups

Table 7 Studies assessed the allograft survival rate comparison between HMP and SCS in the extended donor criteria kidneys

Study	Follow up	SCS (%)	HMP	*P*-value
Jochmans et al. [9]	3 months	96.3	98.8	NS
	1 year	95.1	96.3	NS
Watson al. [10]	1 year	98	93	0.30
Treckmann et al. [11]	1 year	80.2	92.3	0.02
Forde et al. [12]	1 year	96.77	97.85	NS
Gallinat et al. [14]	1 year	88.4	97.7	0.09
Zhong et al. [16]	1 year	93	98	0.026
	3 year	82	93	0.036
Savoye et al. [17]	1 year	Death Cs: 90.8	Death Cs: 92.4	0.32
		No death Cs: 87.6	No death Cs: 88.8	0.12
Foucher al. [18]	5 year	72	64	0.1551
Ravaioli et al. [20]	1 year	93.3	100	0.89
Meister et al. [21]	6 months	Death Cs: 100	Death Cs: 93	0.04
		No death Cs: 100	No death Cs: 87	
Summers et al. [22]	1 year	93.7	96	0.38
Zlatev et al. [23]	3 months	100	83	0.999
Husen et al. [24]	1 year	93.3	92.1	0.71

Discussion

Kidney transplantation remains the gold standard and the only definitive treatment for many people living with end-stage renal disease (ESRD), with the alternative being chronic outpatient dialysis. Those on dialysis are constantly inconvenienced by their hours-long dialysis sessions several times per week and are additionally at a high risk of uremia, poor nutritional status, cardiovascular disease, and infection, which can progress to sepsis and death [25]. While it is generally agreed upon those recipients of extended criteria kidneys have inferior outcomes compared to those of standard criteria kidneys, they do have improved survival compared to dialysis patients who remain on the waitlist, and hence there is demand for them [2]. While effective in cost and outcomes for optimal donor organs, traditional static cold storage (SCS) is less suitable for use in marginal organ transplants, where machine perfusion has several attractive advantages. First, it reduces the chances of ischemic-reperfusion injury (IRI), commonly cited as being responsible for poor transplant outcomes [4]. Second, it allows for additional functional assessment of the organ before implantation rather than relying solely on procurement biopsies, which are often of poor quality, and

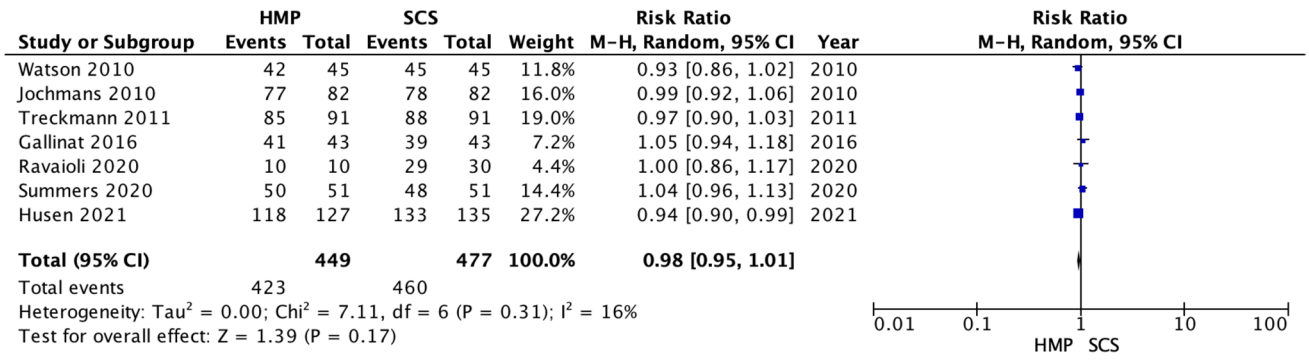

Fig. 4 1-year patient survival comparison between the HMP and SCS groups

donor statistics [5]. Machine perfusion also improves transplant logistics by eliminating the time constraint inherent to traditional cold storage. Finally, machine perfusion may provide the opportunity to introduce medications or other interventions ex vivo to recondition the organ before implantation. All these factors make machine perfusion highly desirable in the pursuit of increasing the utilization of high-risk organs without needing to jeopardize outcomes. The more this technology can be implemented, the further we can get toward the ultimate goal of closing the gap between the supply and demand of viable kidneys for transplant.

Three different types of machine perfusion are currently being looked at for use in kidney transplantation, characterized by their operating temperature.

1. Hypothermic machine perfusion (HMP) is currently the most widely used method. This operates between 4 and 10 °C, which, similarly to SCS, slows down cellular metabolism, reducing oxygen requirements and ATP depletion. Circulation of perfusate provides nutrients to the organ while toxic metabolites generated during warm ischemia or SCS can be flushed [6].
2. Normothermic machine perfusion (NMP) operates between 35 and 37 °C. This means reducing or even eliminating cold ischemia time (CIT) and the harm caused by these low temperatures. However, the physiological temperature also means physiological cellular metabolism, so for NMP to be viable, the perfusate must contain an oxygen carrier in addition to other nutrients or pharmacological interventions [7].
3. Sub normothermic machine perfusion (SNMP) operates between 20 and 32 °C. This middle ground temperature is targeted to avoid both the organ damage caused by cold temperatures and the increase in metabolism that necessitates the use of an oxygen carrier in the perfusate [7].

In the present review, we demonstrated the application of hypothermic machine perfusion use in extended donor criteria kidneys before transplantation and the outcomes compared to the static cold storage technique. Although the number of cases and the duration of follow-ups are limited, the current data is promising. We found a significantly lower DGF rate in kidneys preserved by HMP compared to SCS ($P < 0.00001$). The 1-year allograft survival rate also showed the superiority of HMP compared to SCs for post-discard preservation in the extended donor criteria and marginal kidneys. Although some studies found a better GFR in the kidneys preserved by SCS after the first year. The studies that followed their cases for more than a year saw no difference in terms of GFR. Besides, HMP also improves transplant logistics and allocations by eliminating the time constraint inherent to traditional cold storage and also allows the transplant team to choose the proper operation schedule and time.

Wang et al. [15] conducted a matched clinical trial in 2017 and compared the outcome of patients who received a kidney donated after cardiac death that was preserved either by static cold storage or hypothermic machine perfusion. After 6 months of follow-up, they found a superior outcome for the patients in the hypothermic machine group. Initially, they observed a significantly lower DGF rate in the patients who received a kidney that was preserved by

Table 8 Studies assessed the patient survival rate comparison between HMP and SCS in the extended donor criteria kidneys

Study	Follow up	SCS (%)	HMP (%)	P value
Jochmans et al. [9]	3 months	96.3	96.3	NS
	1 year	95.1	93.9	NS
Watson al. [10]	1 year	100	93	0.08
Treckmann et al. [11]	1 year	96.7	93.4	0.30
Gallinat et al. [14]	1 year	90.7	95.3	0.36
Wang et al. [15]	6 months	100	100	1
Foucher al. [18]	5 year	72	64	0.1551
Ravaioli et al. [20]	1 year	96.6	100	0.391
Summers et al. [22]	1 year	93.7	97.7	0.36
Husen et al. [24]	1 year	98.5	92.9	0.03

a hypothermic machine (16.7% vs. 37.5%, $P=0.03$), similar to what we found in the overall comparison. The length of hospital stay was also significantly lower in this group (12.3 days vs. 19.4 days, $P=0.001$). The serum creatinine was normalized in both groups after 6 months, but it was significantly lower in the patients who received a kidney that was preserved by a hypothermic machine (1.18 vs. 1.46 mg/dl, $P=0.05$). Summers et al. [22] did a similar study in 2020 with more cases in each group. Although all the outcomes were better in the patients who received a kidney that was preserved by a hypothermic machine, the difference was not significant. Husen et al. [24] conducted the same study, but they added oxygen during hypothermic machine perfusion. They reported that they did not see a significant difference between the two groups. Although, they reported a better patient survival rate in the static cold storage group after 1 year of follow-up (98.5% vs. 92.9%, $P=0.03$). Twelve patients from the oxygenated hypothermic machine perfusion died within the first year. They reported that 11 of those patients had a functioning graft at the time of death, and the death was not graft related.

Jochmans et al. [26] clinical trial focused on the effect of adding oxygen during hypothermic machine perfusion. They found that adding oxygen significantly reduces the biopsy-proven acute rejection and 1-year graft survival rate. The kidneys that were preserved with oxygenated hypothermic machine perfusion had 14% BPAR compared to 26% in the non-oxygenated hypothermic machine perfusion group ($P=0.04$). Three percent of grafts failed within a year in the $HMPO_2$ group and 11% in the non-oxygenated hypothermic machine perfusion group ($P=0.02$). Their study focused on one of the most important advantages of machine perfusion compared to the static cold storage method, which is the possibility of doing interventions. They concluded that adding oxygen to the hypothermic machine perfusion can improve the outcomes of marginal kidneys.

Ravaioil et al. [27] study was the first clinical trial that compared the outcome of extended donor criteria kidneys that were preserved by hypothermic oxygenated perfusion (HOPE) and SCS. They reported a significantly higher 1-year graft survival rate when kidneys were preserved using HOPE compared to the SCS group ($P=0.03$). They also reported a higher readmission rate in the SCS group after 6 months ($P=0.04$). Although the results from all the studies about the efficacy of hypothermic machine perfusion in extended donor criteria kidneys are promising in terms of outcomes, some limitations still need further assessments and investigations. Randomized clinical trials can eliminate important biases in the studies, which results in more accurate data collection and outcomes. Due to the shortage of overall available kidneys for transplantation, designing a randomized clinical trial with a significant number of cases needs a strict plan and the collaboration of kidney transplant centers for a multi-institutional project. Normothermic machine perfusion (NMP) is a novel method that has recently grabbed more attention as some studies show a better outcome compared to HMP. Conducting a randomized clinical trial that compares the outcome of the marginal kidneys that were preserved either by SCS or NMP can better demonstrate the efficacy of using machine perfusion in extended donor criteria and so-called marginal kidneys. Although, there are some logistic limitations for the normothermic machines. Currently, a few companies make normothermic machines and have different device protocols and settings. Still, some studies are needed to establish the best setting for the NMP, which can improve the overall outcomes for patients and reduce post transplants complications.

In conclusion, we found that extended donor criteria and marginal kidneys preserved by HMP had a lower DGF rate and better 1-year allograft survival rate. Additionally, recent studies show that these outcomes can even improve by adding oxygen to the HMP during the preservation and have a superiority over the traditional SCS preservation method.

Author Contribution Mahmoudreza Moein and Reza F. Saidi participated in study design. Mahmoudreza Moein, Jonathan Capelin, and Joseph F. Toth were responsible for data collection, analysis, and interpretation. Mahmoudreza Moein and Reza F. Saidi did the critical revision of the article. Mahmoudreza Moein and Jonathan Capelin participated in writing the article.

Data Availability All the available data was provided in tables and no further data was available.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare no competing interests.

References

1. Schütte-Nütgen K, Finke M, Ehlert S, Thölking G, Pavenstädt H, Suwelack B, Palmes D, Bahde R, Koch R, Reuter S. Expanding the donor pool in kidney transplantation: should organs with acute kidney injury be accepted?-a retrospective study. PLoS One. 2019;14(3):e0213608. https://doi.org/10.1371/journal.pone.0213608.
2. Filiopoulos V, Boletis JN. Renal transplantation with expanded criteria donors: which is the optimal immunosuppression? World J Transplant. 2016;6(1):103. https://doi.org/10.5500/wjt.v6.i1.103.
3. King KL, Chaudhry SG, Ratner LE, Cohen DJ, Husain SA, Mohan S. Declined offers for deceased donor kidneys are

not an independent reflection of organ quality. Kidney360. 2021;2(11):1807–18. https://doi.org/10.34067/kid.0004052021.
4. Bellini MI, Tortorici F, Amabile MI, D'Andrea V. Assessing kidney graft viability and its cells metabolism during machine perfusion. Int J Mol Sci. 2021;22(3):1121. https://doi.org/10.3390/ijms22031121.
5. Kasiske BL, Stewart DE, Bista BR, et al. The role of procurement biopsies in acceptance decisions for kidneys retrieved for transplant. Clin J Am Soc Nephrol. 2014;9(3):562–71. https://doi.org/10.2215/cjn.07610713.
6. Yuan X, Theruvath AJ, Ge X, et al. Machine perfusion or cold storage in organ transplantation: indication, mechanisms, and future perspectives. Transpl Int. 2010;23(6):561–70. https://doi.org/10.1111/j.1432-2277.2009.01047.x.
7. Zulpaite R, Miknevicius P, Leber B, Strupas K, Stiegler P, Schemmer P. *Ex-vivo* kidney machine perfusion: Therapeutic potential. Front Med (Lausanne). 2021;24(8):808719. https://doi.org/10.3389/fmed.2021.808719.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
9. Jochmans I, Moers C, Smits JM, Leuvenink HG, Treckmann J, Paul A, Rahmel A, Squifflet JP, van Heurn E, Monbaliu D, Ploeg RJ, Pirenne J. Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. Ann Surg. 2010;252(5):756–64. https://doi.org/10.1097/SLA.0b013e3181ffc256.
10. Watson CJ, Wells AC, Roberts RJ, Akoh JA, Friend PJ, Akyol M, Calder FR, Allen JE, Jones MN, Collett D, Bradley JA. Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. Am J Transplant. 2010;10(9):1991–9. https://doi.org/10.1111/j.1600-6143.2010.03165.x.
11. Treckmann J, Moers C, Smits JM, Gallinat A, Maathuis MH, van Kasterop-Kutz M, Jochmans I, Homan van der Heide JJ, Squifflet JP, van Heurn E, Kirste GR, Rahmel A, Leuvenink HG, Pirenne J, Ploeg RJ, Paul A. Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. Transpl Int. 2011;24(6):548–54. https://doi.org/10.1111/j.1432-2277.2011.01232.x.
12. Forde JC, Shields WP, Azhar M, Daly PJ, Zimmermann JA, Smyth GP, Eng MP, Power RE, Mohan P, Hickey DP, Little DM. Single centre experience of hypothermic machine perfusion of kidneys from extended criteria deceased heart-beating donors: a comparative study. Ir J Med Sci. 2016;185(1):121–5. https://doi.org/10.1007/s11845-014-1235-8.
13. Yao L, Zhou H, Wang Y, Wang G, Wang W, Chen M, Zhang K, Fu Y. Hypothermic machine perfusion in DCD kidney transplantation: a single center experience. Urol Int. 2016;96(2):148–51. https://doi.org/10.1159/000431025.
14. Gallinat A, Amrillaeva V, Hoyer DP, Kocabayoglu P, Benko T, Treckmann JW, van Meel M, Samuel U, Minor T, Paul A. Reconditioning by end-ischemic hypothermic in-house machine perfusion: a promising strategy to improve outcome in expanded criteria donors kidney transplantation. Clin Transplant. 2017;31(3). https://doi.org/10.1111/ctr.12904.
15. Wang W, Xie D, Hu X, Yin H, Liu H, Zhang X. Effect of hypothermic machine perfusion on the preservation of kidneys donated after cardiac death: a single-center, randomized, controlled trial. Artif Organs. 2017;41(8):753–8. https://doi.org/10.1111/aor.12836.
16. Zhong Z, Lan J, Ye S, Liu Z, Fan L, Zhang Y, Fu Z, Qiao B, Shiu-Chung Ko D, Wang Y, Ye Q. Outcome improvement for hypothermic machine perfusion versus cold storage for kidneys from cardiac death donors. Artif Organs. 2017;41(7):647–53. https://doi.org/10.1111/aor.12828.
17. Savoye E, Macher MA, Videcoq M, Gatault P, Hazzan M, Abboud I, Thierry A, Bertrand D, Drouin S, Sayegh J, Barrou B, Badet L, Bastien O, Huot O, Lamotte C, Logerot H, Legeai C, Antoine C. Evaluation of outcomes in renal transplantation with hypothermic machine perfusion for the preservation of kidneys from expanded criteria donors. Clin Transplant. 2019;33(5):e13536. https://doi.org/10.1111/ctr.13536.
18. Foucher Y, Fournier MC, Legendre C, Morelon E, Buron F, Girerd S, Ladrière M, Mourad G, Garrigue V, Glotz D, Lefaucheur C, Cassuto E, Albano L, Giral M, Dantal J, DIVAT Consortium. Comparison of machine perfusion versus cold storage in kidney transplant recipients from expanded criteria donors: a cohort-based study. Nephrol Dial Transplant. 2020;35(6):1043–70. https://doi.org/10.1093/ndt/gfz175.
19. Arlaban M, Barreda P, Ballesteros MA, Rodrigo E, Suberviola B, Valero R, Miñambres E, Ruiz-San Millán JC. Static cold storage vs ex vivo machine perfusion: results from a comparative study on renal transplant outcome in a controlled donation after circulatory death program. Transplant Proc. 2019;51(2):311–3. https://doi.org/10.1016/j.transproceed.2018.12.010.
20. Ravaioli M, De Pace V, Angeletti A, Comai G, Vasuri F, Baldassarre M, Maroni L, Odaldi F, Fallani G, Caraceni P, Germinario G, Donadei C, Malvi D, Del Gaudio M, Bertuzzo VR, Siniscalchi A, Ranieri VM, D'Errico A, Pasquinelli G, Morelli MC, Pinna AD, Cescon M, La Manna G. Hypothermic oxygenated new machine perfusion system in liver and kidney transplantation of extended criteria donors:first Italian clinical trial. Sci Rep. 2020;10(1):6063. https://doi.org/10.1038/s41598-020-62979-9.Erratum.In:SciRep.2020Sep1;10(1):14658.
21. Meister FA, Czigany Z, Rietzler K, Miller H, Reichelt S, Liu WJ, Boecker J, Moeller MJ, Tolba RH, Hamesch K, Strnad P, Boor P, Stoppe C, Neumann UP, Lurje G. Decrease of renal resistance during hypothermic oxygenated machine perfusion is associated with early allograft function in extended criteria donation kidney transplantation. Sci Rep. 2020;10(1):17726. https://doi.org/10.1038/s41598-020-74839-7.
22. Summers DM, Ahmad N, Randle LV, O'Sullivan AM, Johnson RJ, Collett D, Attia M, Clancy M, Tavakoli A, Akyol M, Jamieson NV, Bradley JA, Watson CJE. Cold pulsatile machine perfusion versus static cold storage for kidneys donated after circulatory death: a multicenter randomized controlled trial. Transplantation. 2020;104(5):1019–25. https://doi.org/10.1097/TP.0000000000002907.
23. Zlatev H, von Horn C, Kaths M, Paul A, Minor T. Clinical use of controlled oxygenated rewarming of kidney grafts prior to transplantation by ex vivo machine perfusion. A pilot study. Eur J Clin Invest. 2022;52(2):e13691. https://doi.org/10.1111/eci.13691.
24. Husen P, Boffa C, Jochmans I, Krikke C, Davies L, Mazilescu L, Brat A, Knight S, Wettstein D, Cseprekal O, Banga N, Bellini MI, Szabo L, Ablorsu E, Darius T, Quiroga I, Mourad M, Pratschke J, Papalois V, Mathe Z, Leuvenink HGD, Minor T, Pirenne J, Ploeg RJ, Paul A. Oxygenated end-hypothermic machine perfusion in expanded criteria donor kidney transplant: a randomized clinical trial. JAMA Surg. 2021;156(6):517–25. https://doi.org/10.1001/jamasurg.2021.0949.
25. Himmelfarb J, Ikizler TA. Hemodialysis. N Engl J Med. 2010;363(19):1833–45. https://doi.org/10.1056/NEJMra0902710.
26. Jochmans I, Brat A, Davies L, Hofker HS, van de Leemkolk FEM, Leuvenink HGD, Knight SR, Pirenne J, Ploeg RJ, COMPARE Trial Collaboration and Consortium for Organ Preservation in Europe (COPE). Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE):

a randomised, double-blind, paired, phase 3 trial. Lancet. 2020;396(10263):1653–62. https://doi.org/10.1016/S0140-6736(20)32411-9.

27. Ravaioli M, Germinario G, Dajti G, Sessa M, Vasuri F, Siniscalchi A, Morelli MC, Serenari M, Del Gaudio M, Zanfi C, Odaldi F, Bertuzzo VR, Maroni L, Laurenzi A, Cescon M. Hypothermic oxygenated perfusion in extended criteria donor liver transplantation-A randomized clinical trial. Am J Transplant. 2022. https://doi.org/10.1111/ajt.17115.