Meta-Analysis and Clinical Guidance of Oxygenated Hypothermic Machine Perfusion for Kidney Transplantation

Degong Jia[a,#], Shanshan Guo[b,#], Jiefu Luo[c], Yuezhou Zhang[c], Huiqing Zhang[d], Shengwei[c], and Junyan Liu[c*]

[a]Department of Kidney Transplantation, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [b]School of Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China; [c]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; and [d]Department of Urology, The First Affiliated Hospital of Xinxiang Medical University, Weihui, Henan, China

ABSTRACT

Background. It remains unclear whether oxygenated hypothermic machine perfusion ($HMPO_2$) during kidney preservation is beneficial for prognosis.

Methods. A comprehensive search of databases and clinical trial registries was conducted to identify eligible studies on $HMPO_2$ application during kidney transplantation. A multisubgroup analysis was further conducted to explore the heterogeneity among studies.

Results. Compared to the control treatment, $HMPO_2$ did not significantly alter the incidence of postoperative acute rejection, graft survival, patient mortality, delayed graft function (DGF), functional DGF, primary nonfunction, or estimated glomerular filtration rate, whereas the warm ischemia time appeared to be longer. However, the number of patients with adverse events and the proportion of severe adverse events were reduced in the $HMPO_2$ group. Subgroup analysis indicated that $HMPO_2$ performed better in donation after cardiac death (DCD), and continuous $HMPO_2$ was superior to end-$HMPO_2$.

Conclusion. $HMPO_2$ application during kidney transplantation reduced the number of patients with adverse events and the proportion of severe adverse events. However, given the issue such as limited number of studies and heterogeneity, rigorous evidence studies are needed to further confirm these findings.

THE high prevalence of chronic kidney disease (CKD) has contributed to the increasing burden of end-stage renal disease (ESRD) [1]. Kidney transplantation (KT), compared to other renal replacement therapies such as dialysis, offers a survival advantage and economic benefits, making it the preferred treatment option. However, this has exacerbated the shortage of organs [2,3]. To address the growing organ demand, some transplant centers have resorted to using expanded criteria donors (ECDs) in an attempt to reduce transplant waiting times [4]. However, these kidneys are more susceptible to ischemia–reperfusion injury (IRI), leading to delayed graft function (DGF) and primary nonfunction (PNF) [5−7]. Therefore, efforts have been made to explore organ preservation strategies that can alleviate IRI.

Currently, there are 2 main methods of organ preservation used in clinical practice: static cold storage (SCS) and hypothermic machine perfusion (HMP). Both methods aim to reduce the metabolic rate and oxygen demand of the organs to alleviate the harm caused by ischemia [8]. A meta-analysis has shown that compared to SCS, the use of HMP significantly reduces the incidence of DGF, and overall treatment costs are lower [9]. However, during HMP, hypoxia is still common, as the storage solution is not actively oxygenated [10]. In large animal models, active oxygenation during HMP can significantly reduce renal oxidative stress levels, improve early postoperative renal function, and mitigate renal fibrosis [11−13]. Therefore, whether oxygenated hypothermic machine perfusion ($HMPO_2$) can play a beneficial role in clinical KT has attracted widespread attention [14,15]. Unfortunately, existing studies have not yet reached a definitive consensus.

[#] Degong Jia and Shanshan Guo contributed equally to this article.

*Address correspondence to Junyan Liu, MD, Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, No.76, Linjiang Road, Chongqing, 400010, China. E-mail: 2022110339@stu.cqmu.edu.cn

0041-1345/20
https://doi.org/10.1016/j.transproceed.2025.03.006

230 Park Avenue, New York, NY 10169

To further clarify whether $HMPO_2$, as an optimized organ preservation method, can improve renal transplant outcomes, we conducted this meta-analysis.

PATIENTS AND METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [16] and Assessing the methodological quality of systematic reviews (AMSTAR) guidelines, and registered in PROSPERO (CRD42023412502).

STUDY DESIGN AND SEARCH STRATEGY

A comprehensive search was conducted in databases including MEDLINE, Embase, Cochrane Library, and relevant online clinical trial registries such as ClinicalTrial.gov and the World Health Organization International Clinical Trials Registry Platform.

STUDY SELECTION

The inclusion criteria were original studies that used $HMPO_2$ for kidney preservation, with SCS or other organ preservation methods such as HMP as the control. Case reports, reviews, composite transplantation studies, multiorgan transplantation studies, and studies that did not provide sufficient clinical information to assess the impact of $HMPO_2$ were excluded. Studies with fewer than 5 participants were also excluded [17].

RISK OF BIAS ASSESSMENT

The quality assessment for observational studies was conducted using the Newcastle−Ottawa Quality Assessment Scale and randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias Assessment Tool.

DATA EXTRACTION

Two authors (JDG and GSS) independently conducted data extraction using a specifically designed data extraction form for eligible clinical studies. Continuous variables were collected as the mean and standard deviation (SD), while dichotomous variables were collected as the number of positive events and total events. Discrepancies in data extraction were resolved through discussion or involvement of a third author (LJY).

DATA SYNTHESIS AND ANALYSIS

The predefined primary outcomes were graft survival and acute rejection, and secondary outcomes included DGF, PNF, postoperative complications, patient mortality, the estimated glomerular filtration rate, and the graft ischemia time.

A meta-analysis was conducted using Review Manager version 5.4, and the report followed the PRISMA guidelines. Dichotomous variables are presented herein as risk ratios (RR) with 95% confidence intervals (CI), and continuous variables are expressed as the mean differences (MD). Forest plots were used for visual representation of the analysis results, with statistical significance considered when $P < .05$.

Heterogeneity among studies was evaluated using the χ^2 test and I^2 statistic, with $P_{Heterogeneity} < 0.01$ or $I^2 > 50\%$ indicating significant heterogeneity among studies. In the presence of heterogeneity, a random-effects model was used to summarize the study results; otherwise, a fixed-effects model was used.

SUBGROUP ANALYSIS

This investigation is the first to explore the duration, oxygen concentration, and suitable populations of $HMPO_2$. Stratification was performed based on long-term continuous $HMPO_2$ and short-term end-$HMPO_2$ to identify the optimal use pattern. The oxygen concentration (21% or 100%) was conducted to explore the optimal oxygen content for $HMPO_2$. Studies were also stratified based on different patient populations, including donation after brain death (DBD) and donation after cardiac death (DCD).

RESULTS

Summary of the included studies

After excluding duplicate articles, a total of 1490 articles were screened for abstracts and full texts. The PRISMA flowchart for the included studies is presented in Fig 1. Ultimately, 5 studies met the inclusion criteria, with a total of 662 participants, of whom 309 received donor kidneys preserved through $HMPO_2$ [14,15,18−20]. Detailed information on each study can be found in the characteristics table of the included studies (Table 1 and Supplementary Table S2). A summary of the study results is presented in Table 2. The results of the multi-subgroup analysis are summarized in Table 3.

The risk of bias information for the studies is summarized in Figure 2. Overall, none of the studies showed a poor design, as they were relevant to our study population and outcomes of interest.

Primary Outcomes

Acute Rejection. Four studies reported the incidence of postoperative acute rejection. $HMPO_2$ did not significantly improve the occurrence of acute rejection (RR: 0.94, 95% CI: 0.65-1.35, $P = .72$) (Fig 3A).

Graft Survival. Two studies described graft survival at 6 months postoperatively, and $HMPO_2$ did not improve graft survival at this time point (RR: 0.98, 95% CI: 0.79-1.21, $P = .83$) (Fig 3B). Three studies described graft survival at 1 year postoperatively, and there was no improvement in graft survival at 1 year with $HMPO_2$ (RR: 1.03, 95% CI: 0.98-1.08, $P = .23$) (Fig 3C).

Secondary Outcomes

Delayed Graft Function. We primarily analyzed the impact of $HMPO_2$ on DGF and functional DGF. Five studies described the incidence of DGF, and $HMPO_2$ did not reduce the occurrence

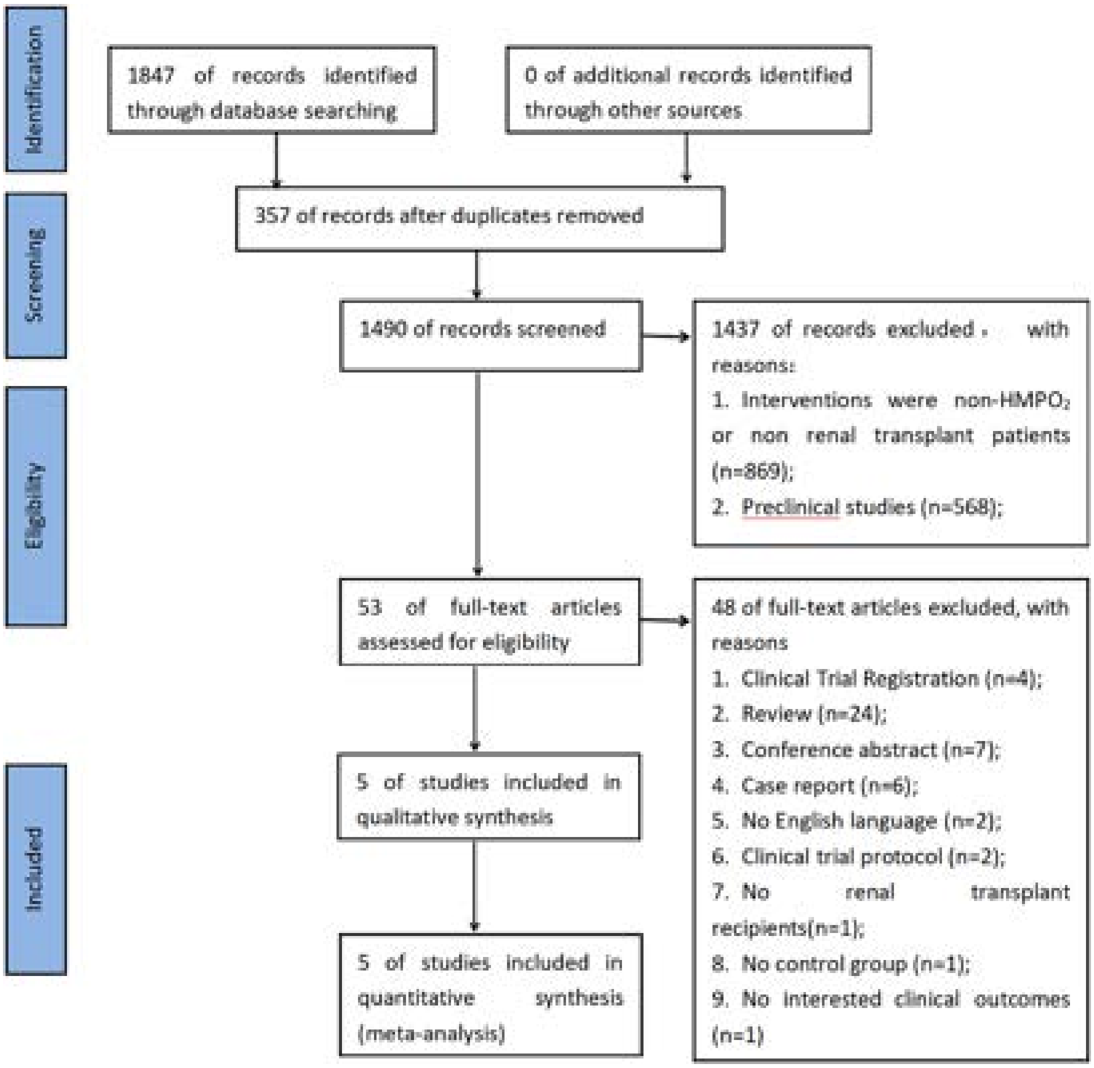


Fig 1. PRISMA flow chart for meta-analysis literature retrieval and study selection. $HMPO_2$, oxygenated hypothermic machine perfusion.

of DGF (RR: 0.93, 95% CI: 0.74-1.18, *P* = .56) (Fig 4A). Two robust studies described functional DGF, and the combined analysis suggested no reduction in functional DGF with $HMPO_2$ (RR: 0.93, 95% CI: 0.82-1.05, *P* = .25) (Fig 4B).

Primary Nonfunction. Five studies described the incidence of PNF, and the meta-analysis did not find an association between $HMPO_2$ and PNF (RR: 1.01, 95% CI: 0.49-2.06, *P* = 0.99) (Fig 4C).

Table 1. Characteristics of the Included Studies in This Systematic Review and Meta-analysis.

Author,Year	No. Of Patients	Donor type	the Mode of $HMPO_2$	Oxygen Concentration	Study Type
Peri Husen, 2021	262	DBD	End-$HMPO_2$	100%	Multi-center RCT
Ina Jochmans, 2020	212	DCD	Continue-$HMPO_2$	100%	Multi-center RCT
FranziskaA. Meister, 2020	45	DBD	End-$HMPO_2$	100%	Single-center case-matched study
Riccardo Pravisani, 2022	103	No DCD	End-$HMPO_2$	21%	Single-center cohort study
Matteo Ravaioli, 2020	40	DBD	End-$HMPO_2$	100%	Single-center case-matched study

DBD, donation after brain death; DCD, donation after circulatory death; $HMPO_2$, oxygenated hypothermic machine perfusion preservation; RCT, randomized controlled trials.

Table 2. Summary of the Results of the Meta-Analysis of the Efficacy of HMPO$_2$ in RT

Outcomes	No. of Included Studies	Total Number of DEX and Control	Heterogeneity	Effect Estimation	P-Value
Acute rejection	4	294 of HMPO$_2$ and 323 of control	I^2 47%	RR 0.94 95%CI 0.65 to 1.35	.72
Graft survival					
6-month	2	121 of HMPO$_2$ and 136 of control	I^2 72%	RR 0.98 95%CI 0.79 to 1.21	.83
1-year	3	243 of HMPO$_2$ and 271 of control	I^2 38%	RR 1.03 95%CI 0.98 to 1.08	.23
DGF	5	309 of HMPO$_2$ and 353 of control	I^2 0%	RR 0.93 95%CI 0.74 to 1.18	.56
Functional DGF	2	233 of HMPO$_2$ and 241 of control	I^2 20%	RR 0.93 95%CI 0.82 to 1.05	.25
PNF	5	309 of HMPO$_2$ and 353 of control	I^2 0%	RR 1.01 95%CI 0.49 to 2.06	0.99
Adverse event patients	2	233 of HMPO$_2$ and 241 of control	I^2 47%	RR 0.73 95%CI 0.60 to 0.88	0.001
CD grade>3 complication patients	2	61 of HMPO$_2$ and 82 of control	I^2 23%	RR 0.94 95%CI 0.47 to 1.87	0.85
severe complication rate	2	450 of HMPO$_2$ and 601 of control	I^2 0%	RR 0.70 95%CI 0.51 to 0.96	0.03
Patient death					
6-month	2	121 of HMPO$_2$ and 136 of control	I^2 0%	RR 1.42 95%CI 0.54 to 3.74	0.48
1-year	3	243 of HMPO$_2$ and 271 of control	I^2 44%	RR 1.59 95%CI 0.76 to 3.33	0.22
Egfr					
7-day	2	142 of HMPO$_2$ and 165 of control	I^2 94%	MD -7.64 95% CI -25.46 to 10.19	0.40
3-month	3	230 of HMPO$_2$ and 253 of control	I^2 0%	MD -1.14 95% CI -4.06 to 1.78	0.44
6-month	3	225 of HMPO$_2$ and 248 of control	I^2 51%	MD -1.80 95% CI -7.01 to 3.41	0.50
1-year	2	210 of HMPO$_2$ and 218 of control	I^2 58%	MD 0.74 95% CI -4.51 to 5.98	0.78
CIT	5	295 of HMPO$_2$ and 367 of control	I^2 0%	MD -0.04 95% CI -0.64 to 0.57	0.91
WIT	3	179 of HMPO$_2$ and 231 of control	I^2 0%	MD 2.80 95% CI 0.14 to 5.45	0.04

DGF, delayed graft function; PNF, primary non-function; HMPO$_2$, oxygenated hypothermic machine perfusion; CIT, cold ischemia time; WIT, warm ischemia time; CD, Clavien Dindo; eGFR, estimated glomerular filtration rate.

Table 3. Summary of the Results of the Subgroup Analysis of HMPO$_2$ in RT

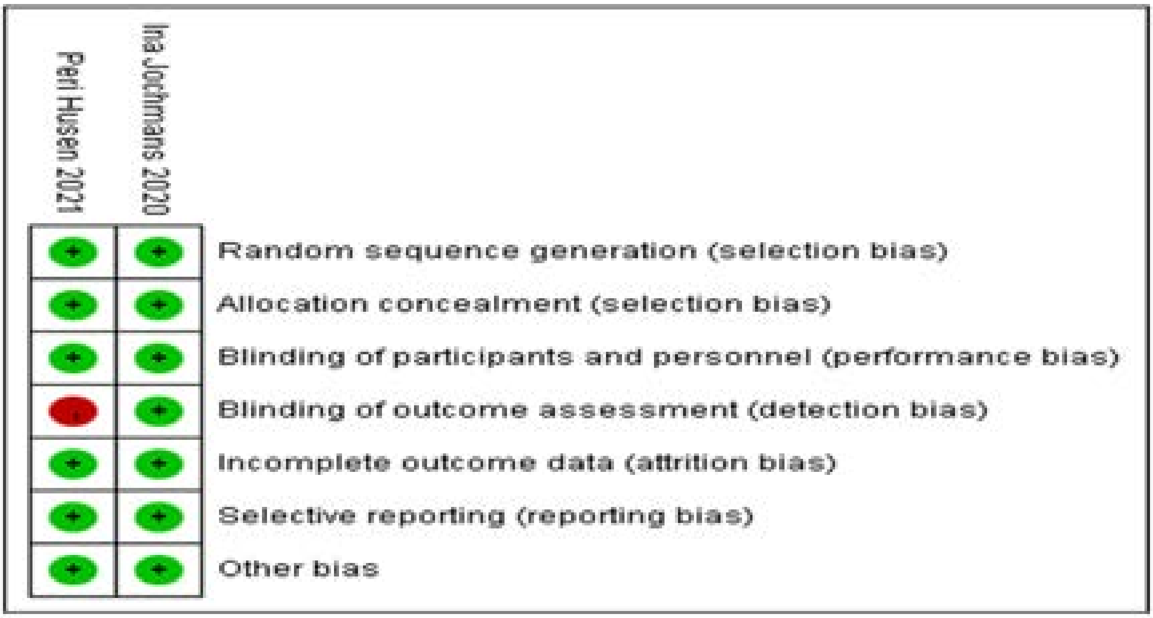
Outcome	Subgroup	No. of Studies	Population size	Effect Estimation (95% CI)	I^2 Statistic (%)
Acute rejection	DBD	2	302	0.79 to 2.37	0
	DCD	1	212	0.31 to 0.98	–
	END-HMPO$_2$	3	405	0.85 to 2.30	0
	CON-HMPO$_2$	1	212	0.31 to 0.98	–
	PO$_2$ 100%	3	514	0.60 to 1.30	60
	PO$_2$ 21%	1	103	0.46 to 5.10	–
1-year graft survival	DBD	2	302	0.93 to 1.06	0
	DCD	1	212	1.00 to 1.17	–
	END-HMPO$_2$	2	302	0.93 to 1.06	0
	CON-HMPO$_2$	1	212	1.00 to 1.17	–
Delayed graft function	DBD	3	347	0.64 to 1.27	43
	DCD	1	212	0.70 to 1.43	–
	END-HMPO$_2$	4	450	0.66 to 1.22	16
	CON-HMPO$_2$	1	212	0.70 to 1.43	–
	PO$_2$ 100%	4	559	0.74 to 1.21	15
	PO$_2$ 21%	1	103	0.43 to 1.74	–
Primary non-function	DBD	3	347	0.53 to 2.88	0
	DCD	1	212	0.15 to 2.45	–
	END-HMPO$_2$	4	450	0.53 to 2.88	0
	CON-HMPO$_2$	1	212	0.15 to 2.45	–
	PO$_2$ 100%	4	559	0.49 to 2.06	0
	PO$_2$ 21%	1	103	–	–
1-year patient death	DBD	2	302	0.99 to 13.62	0
	DCD	1	212	0.33 to 2.33	–
	END-HMPO$_2$	2	302	0.99 to 13.62	0
	CON-HMPO$_2$	1	212	0.33 to 2.33	–
3-month eGFR	DBD	2	307	−5.89 to 1.17	0
	DCD	1	176	−3.69 to 6.69	–
	END-HMPO$_2$	2	307	−5.89 to 1.17	0
	CON-HMPO$_2$	1	176	−3.69 to 6.69	–

(*continued*)

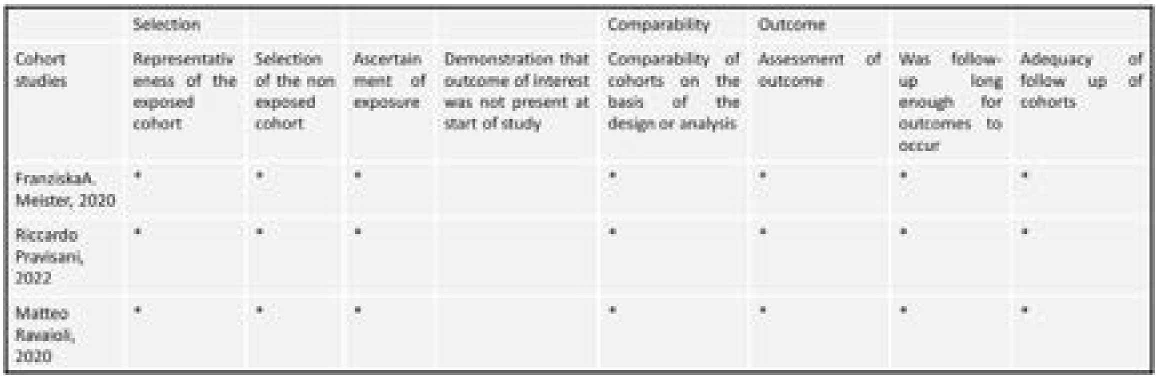
Table 3 (*Continued*)

Outcome	Subgroup	No. of Studies	Population size	Effect Estimation (95% CI)	I^2 Statistic (%)
6-month eGFR	DBD	2	307	−8.47 to -0.03	0
	DCD	1	166	−2.80 to 8.80	–
	END-$HMPO_2$	2	307	−8.47 to -0.03	0
	CON-$HMPO_2$	1	166	−2.80 to 8.80	–
Cold ischemia time	DBD	3	347	−0.62 to 1.29	0
	DCD	1	212	−0.99 to 1.05	–
	END-$HMPO_2$	4	450	−0.82 to 0.68	0
	CON-$HMPO_2$	1	212	−0.99 to 1.05	–
	PO_2 100%	4	559	−0.50 to 0.89	0
	PO_2 21%	1	103	−1.96 to 0.48	–
Warm ischemia time	PO_2 100%	2	307	−0.75 to 5.22	0
	PO_2 21%	1	103	−0.87 to 10.73	–

DBD, donation after brain death; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; $HMPO_2$, oxygenated hypothermic machine perfusion.



Peri Husen 2021	Ina Jochmans 2020	
+	+	Random sequence generation (selection bias)
+	+	Allocation concealment (selection bias)
+	+	Blinding of participants and personnel (performance bias)
−	+	Blinding of outcome assessment (detection bias)
+	+	Incomplete outcome data (attrition bias)
+	+	Selective reporting (reporting bias)
+	+	Other bias



	Selection				Comparability	Outcome		
Cohort studies	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
FranziskaA. Meister, 2020	*	*	*		*	*	*	*
Riccardo Pravisani, 2022	*	*	*		*	*	*	*
Matteo Ravaioli, 2020	*	*	*		*	*	*	*

Fig 2. Quality evaluation results of the included studies.

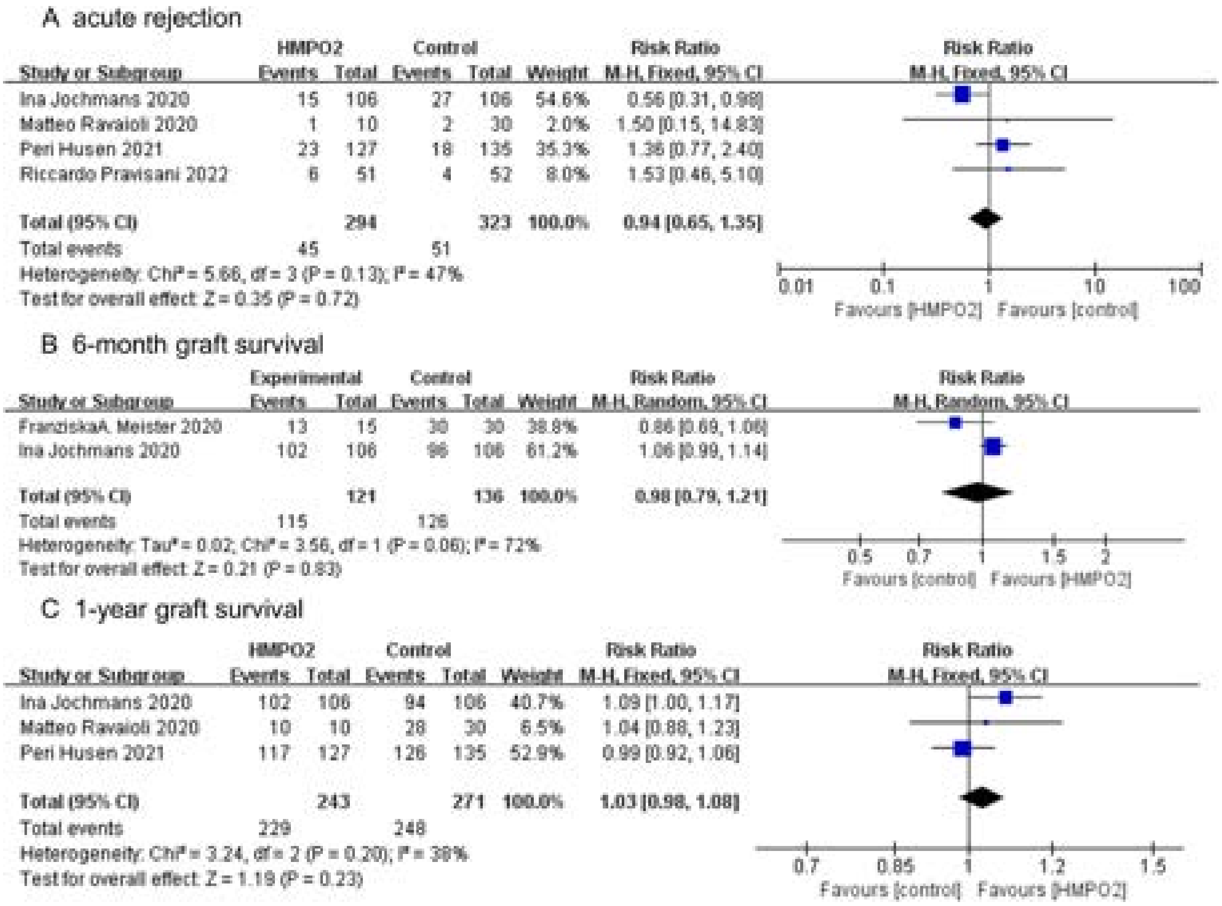


Fig 3. Forest plot of the impact of $HMPO_2$ on acute rejection (A), 6-month (B) and 1-year graft survival (C). Compared with the control, $HMPO_2$ had no significant effect on postoperative acute rejection and graft survival.

POSTOPERATIVE COMPLICATIONS

We analyzed postoperative complications based on the number of patients with adverse events, the number of patients with Clavien−Dindo grade >3 complications, and the proportion of severe adverse events. Two major studies described the number of patients with adverse events, and the meta-analysis showed a significant reduction in the number of patients with postoperative adverse events with $HMPO_2$ (RR: 0.73, 95% CI: 0.60-0.88, *P* = .001) (Fig 5A). Two studies described the occurrence of Clavien−Dindo grade >3 complications, and $HMPO_2$ did not reduce the number of patients with severe complications (RR: 0.94, 95% CI: 0.47-1.87, *P* = .87) (Fig 5B). Two studies described the proportion of severe adverse events, and $HMPO_2$ significantly reduced the occurrence of severe adverse events postoperatively (RR: 0.70, 95% CI: 0.51-0.96, *P* = .03) (Fig 5C).

PATIENT DEATH

We analyzed patient mortality at 6 months and 1 year postoperatively. The meta-analysis did not find an impact of $HMPO_2$ on patient mortality at 6 months (RR: 1.42, 95% CI: 0.54-3.74, *P* = .48) (Fig 6A) and 1 year (RR: 1.59, 95% CI: 0.76-3.33, *P* = .22) (Fig 6B).

ESTIMATED GLOMERULAR FILTRATION RATE

The analysis included the postoperative eGFR at 7 days, 3 months, 6 months, and 1 year. The meta-analysis showed no significant differences in eGFR between the 2 groups at each time point (7-day: MD: -7.64, 95% CI: -25.46 to 10.19, *P* = .40; 3-month: MD: -1.14, 95% CI: -4.06 to 1.78, P=0.44; 6-month: MD: -1.80, 95% CI: -7.01 to 3.41, *P* = .50; 1-year: MD: 0.74, 95% CI: -4.51 to 5.98, *P* = .78) (Fig 7).

GRAFT ISCHEMIA TIME

We analyzed the cold and warm ischemia times of the graft. Five studies described the cold ischemia time (CIT). The meta-analysis results indicated no difference in CIT between the $HMPO_2$ and control groups (MD: -0.04, 95% CI: -0.64 to 0.57, *P* = .91) (Fig 8A).

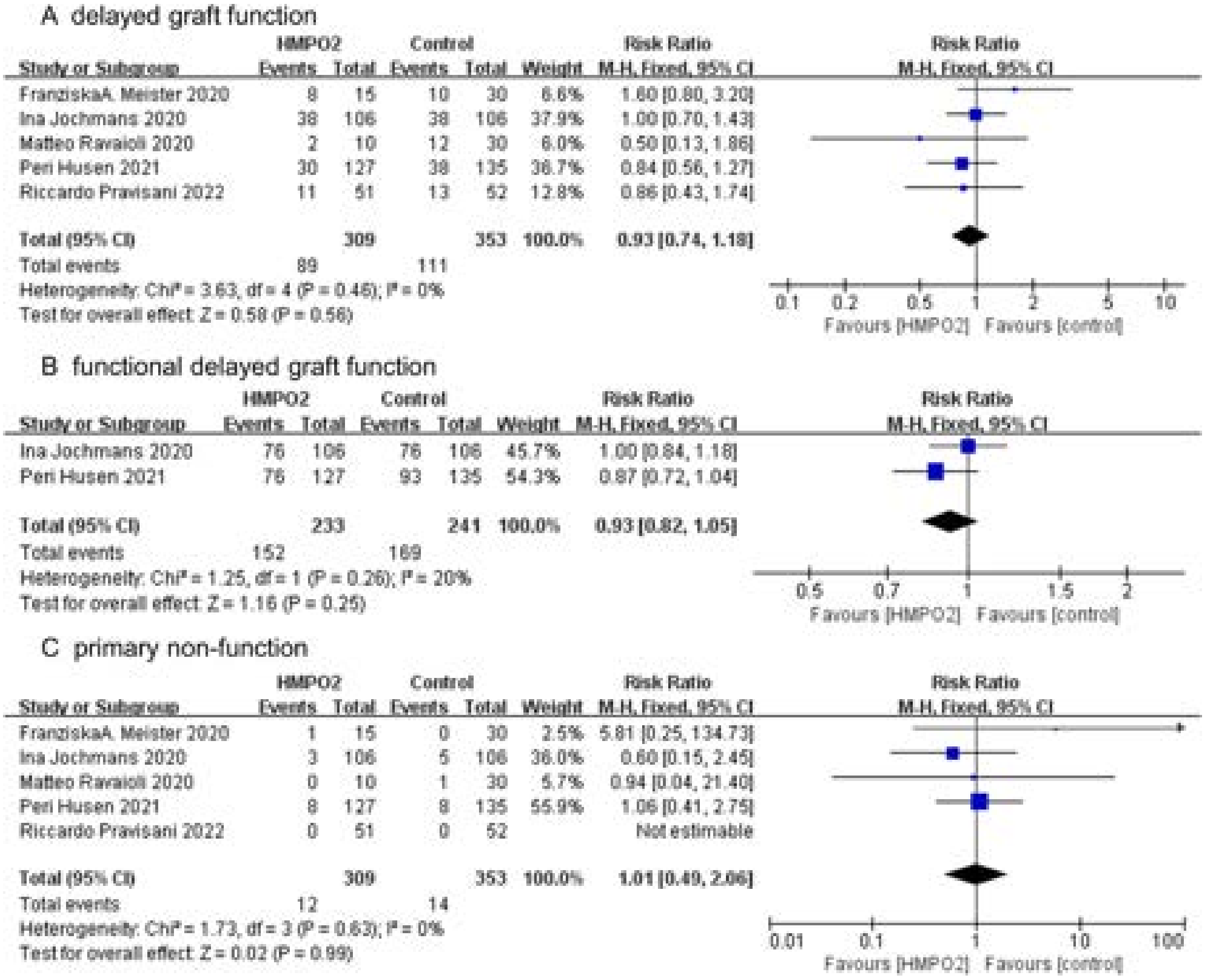


Fig 4. Forest plot of the impact of $HMPO_2$ on DGF (A), functional DGF (B), and PNF (C). The incidence of DGF, functional DGF, and PNF in the $HMPO_2$ group was similar to that in the control group. DGF, delayed graft function; PNF, primary nonfunction.

Three studies described the WIT, and the pooled analysis showed that the WIT was significantly longer in the $HMPO_2$ group than in the control group (MD: 2.80, 95% CI: 0.14-5.45, *P* = .04) (Fig 8B).

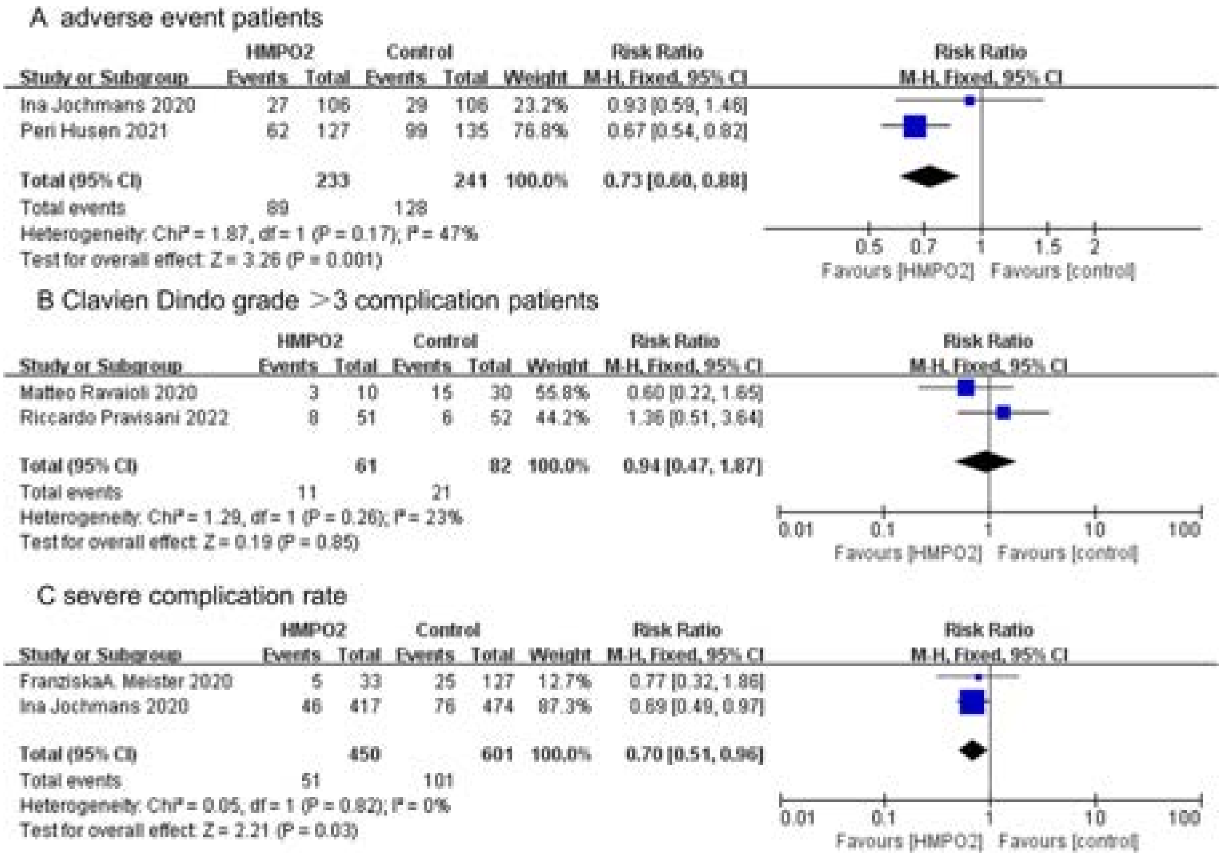
Subgroup Analysis

To explore the optimal patient population, duration time and oxygen concentration for $HMPO_2$, we conducted subgroup analyses (Table 3). First, we found that $HMPO_2$ reduced the incidence of acute rejection in the DCD group (RR: 0.56, 95% CI: 0.31-0.98, *P* = .04) and improved the 1-year graft survival (RR: 1.09, 95% CI: 1.00-1.17, *P* = .04). However, $HMPO_2$ increased the 1-year patient mortality in the DBD group (RR: 3.67, 95% CI: 0.99-13.62, *P* = .05) and decreased the 6-month eGFR (MD: -4.25, 95% CI: -8.47 to -0.03, *P* = .05). Second, the continuous $HMPO_2$ group had a lower incidence of acute rejection (RR: 0.56, 95% CI: 0.31-0.98, *P* = .04) and a higher 1-year graft survival rate (RR: 1.09, 95% CI: 1.00-1.17, *P* = .04), while the end-$HMPO_2$ group had a higher 1-year patient mortality rate (RR: 3.67, 95% CI: 0.99-13.62, *P* = .05) and a lower 6-month eGFR (MD: -4.25, 95% CI: -8.47 to -0.03, *P* = .05). Finally, we did not find any significant impact of different oxygen concentrations on clinical outcomes.

These results suggested that the continuous $HMPO_2$ and DCD populations had better clinical outcomes, while the oxygen concentration did not affect the efficacy of $HMPO_2$.

DISCUSSION

To our knowledge, this is the first meta-analysis examining the role of $HMPO_2$ in KT, encompassing a total of five studies with 662 participants. The results indicate that $HMPO_2$ does not have a significant impact on postoperative acute rejection, survival rates or postoperative renal function. However, $HMPO_2$ does lead to a reduction in the number of patients experiencing adverse events and in the proportion of severe adverse events.



A adverse event patients

Study or Subgroup	HMPO2 Events	HMPO2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ina Jochmans 2020	27	106	29	106	23.2%	0.93 [0.59, 1.46]
Peri Husen 2021	62	127	99	135	76.8%	0.67 [0.54, 0.82]
Total (95% CI)		**233**		**241**	**100.0%**	**0.73 [0.60, 0.88]**
Total events	89		128			

Heterogeneity: Chi² = 1.87, df = 1 (P = 0.17); I² = 47%

Test for overall effect: Z = 3.26 (P = 0.001)

B Clavien Dindo grade >3 complication patients

Study or Subgroup	HMPO2 Events	HMPO2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Matteo Ravaioli 2020	3	10	15	30	55.8%	0.60 [0.22, 1.65]
Riccardo Pravisani 2022	8	51	6	52	44.2%	1.36 [0.51, 3.64]
Total (95% CI)		**61**		**82**	**100.0%**	**0.94 [0.47, 1.87]**
Total events	11		21			

Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%

Test for overall effect: Z = 0.19 (P = 0.85)

C severe complication rate

Study or Subgroup	HMPO2 Events	HMPO2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FranziskaA. Meister 2020	5	33	25	127	12.7%	0.77 [0.32, 1.86]
Ina Jochmans 2020	46	417	76	474	87.3%	0.69 [0.49, 0.97]
Total (95% CI)		**450**		**601**	**100.0%**	**0.70 [0.51, 0.96]**
Total events	51		101			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 2.21 (P = 0.03)

Fig 5. Forest plot of the impact of $HMPO_2$ on adverse event patients (A), Clavien–Dindo grade >3 complications in patients (B), and the severe adverse event rate (C). Compared with the control, $HMPO_2$ reduced the number of patients with adverse events and the proportion of severe adverse events but had no effect on the number of patients with Clavien–Dindo grade >3 complications.

Therefore, $HMPO_2$ can serve as an alternative organ storage method.

The theoretical addition of oxygen to HMP aims to enhance its benefits by replenishing ATP during the ischemic period. However, this meta-analysis demonstrates that $HMPO_2$ does not affect postoperative acute rejection or graft survival. The use of $HMPO_2$ leads to a transition of cells from anaerobic to aerobic metabolism, reducing the release of reactive oxygen species (ROS) and mitochondrial damage, resulting in a decreased immune response and ultimately leading to a decrease in the occurrence of acute rejection [21,22]. $HMPO_2$ is also the only independent predictor of acute rejection when compared to risk factors such as human leukocyte antigen mismatch and induction therapy with tacrolimus [23,24]. Furthermore, studies indicate that active oxygenation during HMP reduces the generation of damage-associated molecular patterns, the production of mitochondrial superoxide, and the activation of endothelial cells, macrophages, and T cells after reperfusion, thereby impacting graft survival [23,25,26]. Several factors may contribute to these contradictory results. First, the lower incidence of acute rejection due to the use of effective immunosuppressive agents in the 1980s may have minimized the potential impact of $HMPO_2$, making its effectiveness less apparent [27]. Second, the limited number of current studies and uncontrolled confounding factors may have hindered the meta-analysis from accurately elucidating the role of $HMPO_2$, leading to false-negative results. Future RCTs should be conducted to further investigate this matter.

Regarding the investigation of secondary outcomes, we found that $HMPO_2$ reduces the number of patients experiencing adverse events and the proportion of severe adverse events. The possible reason behind this finding is that $HMPO_2$ preconditioning promotes hemodynamic stability during the reperfusion process and prevents electrolyte imbalances such as hyperkalemia [28]. Additionally, $HMPO_2$ leads to a decrease in ROS production during reperfusion, altering oxidative stress and energy status in the transplanted kidney [13]. Ultimately, $HMPO_2$ affects postoperative complications.

Interestingly, the $HMPO_2$ group had a longer WIT. Generally, the WIT is associated with the surgical technique of a transplant center and is usually considered a fixed duration. Additionally, the use of $HMPO_2$ occurs during the cold ischemia phase after warm ischemia, so this outcome might be a false

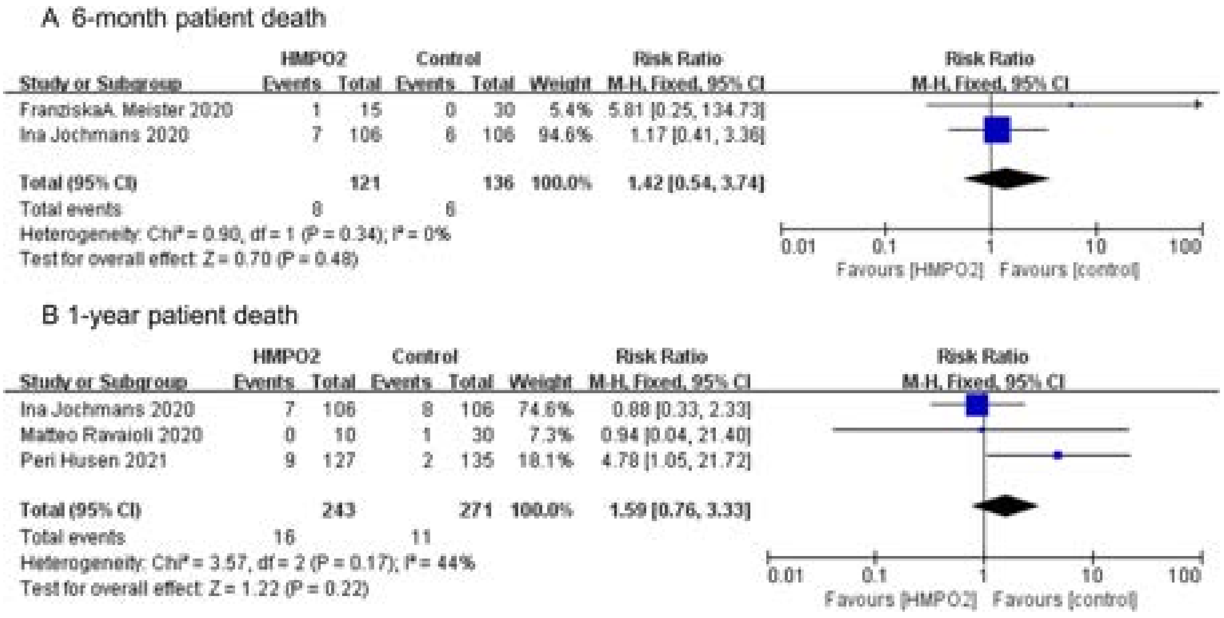


Fig 6. Forest plot of the impact of $HMPO_2$ on 6-month (A) and 1-year patient deaths (B). Compared with the control, $HMPO_2$ had no significant effect on patient deaths.

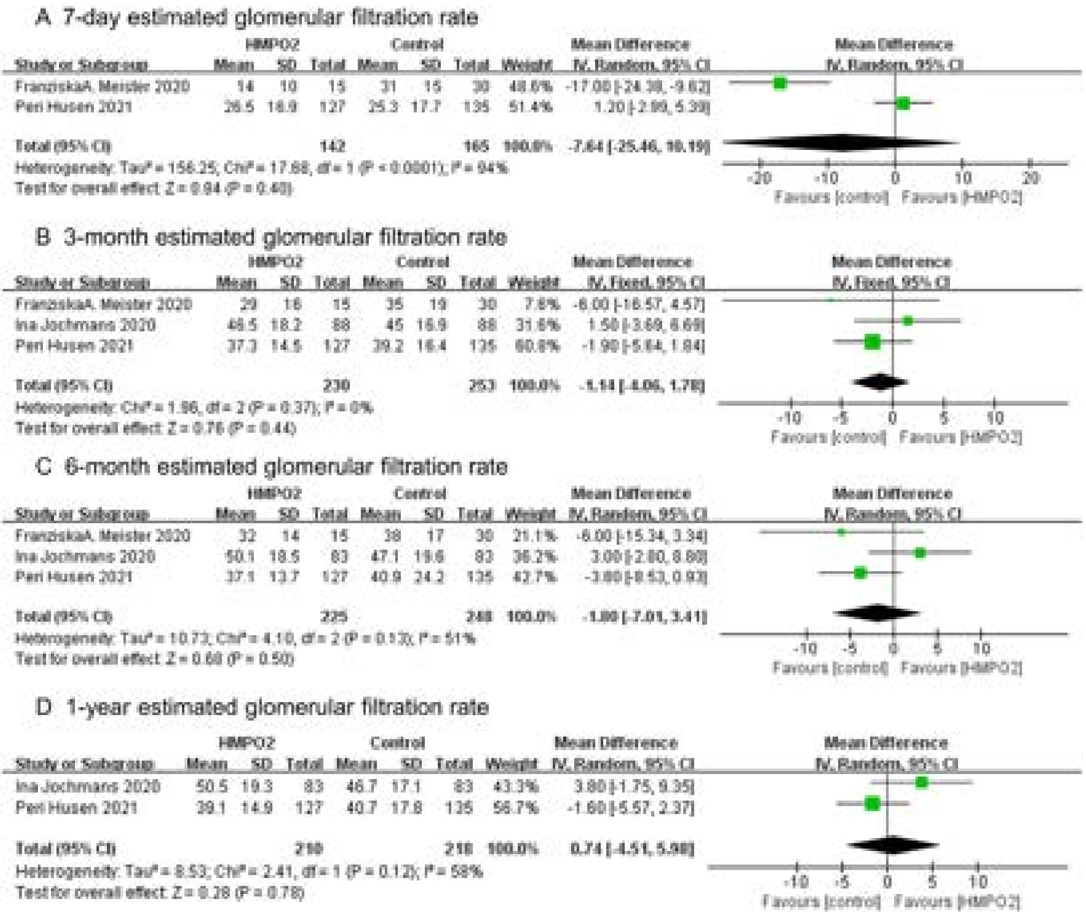
positive. The pooled analysis of only 3 studies is insufficient to accurately determine the effect of $HMPO_2$ on WIT.

We conducted stratified analyses based on different populations, $HMPO_2$ durations, and oxygen concentrations. We found that $HMPO_2$ had some benefits in the DCD group, while the treatment effect in the DBD group seemed less favorable. This outcome could be attributed to the physiological differences between DBD and DCD donors [29]. DCD kidneys are more prone to ischemic cascade and reperfusion injury, leading to a high incidence of postoperative complications compared to that in DBD kidneys. The use of $HMPO_2$ effectively overcomes this physiological disadvantage in DCD [30]. Additionally, continuous $HMPO_2$ appears to have better clinical outcomes and fewer side effects than end-$HMPO_2$. The interpretation of this outcome is that end-$HMPO_2$ utilizes the valuable time when the organ reaches the recipient center to dynamically repair the cold-stored organ. However, determining the exact balance time between SCS and $HMPO_2$ that generates positive clinical outcomes during organ storage is challenging, and different durations of machine perfusion after SCS can lead to different postoperative outcomes [31,32]. Therefore, we recommend that future research focus more on continuous $HMPO_2$. Regarding the oxygen concentration during $HMPO_2$, there is still controversy. Animal experiments have shown that different oxygen concentrations can result in varying levels of ROS, and the oxygen concentration has correlations with organ metabolism and tissue structure, which in turn affect postoperative graft recovery [12,33]. However, we did not find any significant impact of different oxygen concentrations during $HMPO_2$ on clinical outcomes in renal transplant patients. The one small study using a 21% oxygen tension is insufficient for concluding that 21% and 100% oxygen tensions have the same clinical benefits. Further research is needed to explore this aspect in more detail.

STRENGTHEN AND LIMITATION

Our study is the first to provide the most comprehensive synthesis of clinical evidence on the use of HMPO2 for kidney preservation. Notably, two of the included studies were multicenter trials led by the COMPARE Trial Collaboration and Consortium for Organ Preservation in Europe (COPE), with high-quality research enhancing the reliability of this meta-analysis. In this meta-analysis, we elucidated the role of HMPO2 in KT and explored its duration time, oxygen concentration, and target populations. Importantly, all the studies included in our meta-analysis were published within the last 5 years, which enhances the relevance and applicability of this meta-analysis.

This meta-analysis has several limitations. First, most of the included studies analyzed the impact of $HMPO_2$ on acute rejection but lacked information on relevant factors such as calcium-phosphorus levels, donor-specific antibody titers, and proteinuria levels. Future research should consider collecting these necessary data to conduct a more in-depth analysis of the effects of $HMPO_2$ on recipient immune rejection. Second, the included studies used HMP or SCS as controls, and it would be important to compare $HMPO_2$ with other emerging perfusion strategies in future research. Third, there is a relative scarcity of clinical studies related to HMPO2, and the limited research reports and uncontrolled confounding factors may introduce bias into the results of the meta-analysis. RCT studies should be designed to address this issue. Fourth, most studies on end-$HMPO_2$ did not provide details on the duration of $HMPO_2$, making it challenging for subsequent research to reference or avoid the application



A 7-day estimated glomerular filtration rate

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
FranziskaA. Meister 2020	14	10	15	31	15	30	48.6%	-17.00 [-24.38, -9.62]
Peri Husen 2021	26.5	16.9	127	25.3	17.7	135	51.4%	1.20 [-2.99, 5.39]
Total (95% CI)			142			165	100.0%	-7.64 [-25.46, 10.19]

Heterogeneity: Tau² = 156.25; Chi² = 17.88, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.84 (P = 0.40)

B 3-month estimated glomerular filtration rate

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FranziskaA. Meister 2020	29	16	15	35	19	30	7.6%	-6.00 [-16.57, 4.57]
Ina Jochmans 2020	46.5	18.2	88	45	16.9	88	31.6%	1.50 [-3.69, 6.69]
Peri Husen 2021	37.3	14.5	127	39.2	16.4	135	60.8%	-1.90 [-5.64, 1.84]
Total (95% CI)			230			253	100.0%	-1.14 [-4.06, 1.78]

Heterogeneity: Chi² = 1.96, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.44)

C 6-month estimated glomerular filtration rate

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
FranziskaA. Meister 2020	32	14	15	38	17	30	21.1%	-6.00 [-15.34, 3.34]
Ina Jochmans 2020	50.1	18.5	83	47.1	19.6	83	36.2%	3.00 [-2.80, 8.80]
Peri Husen 2021	37.1	13.7	127	40.9	24.2	135	42.7%	-3.80 [-8.53, 0.93]
Total (95% CI)			225			248	100.0%	-1.80 [-7.01, 3.41]

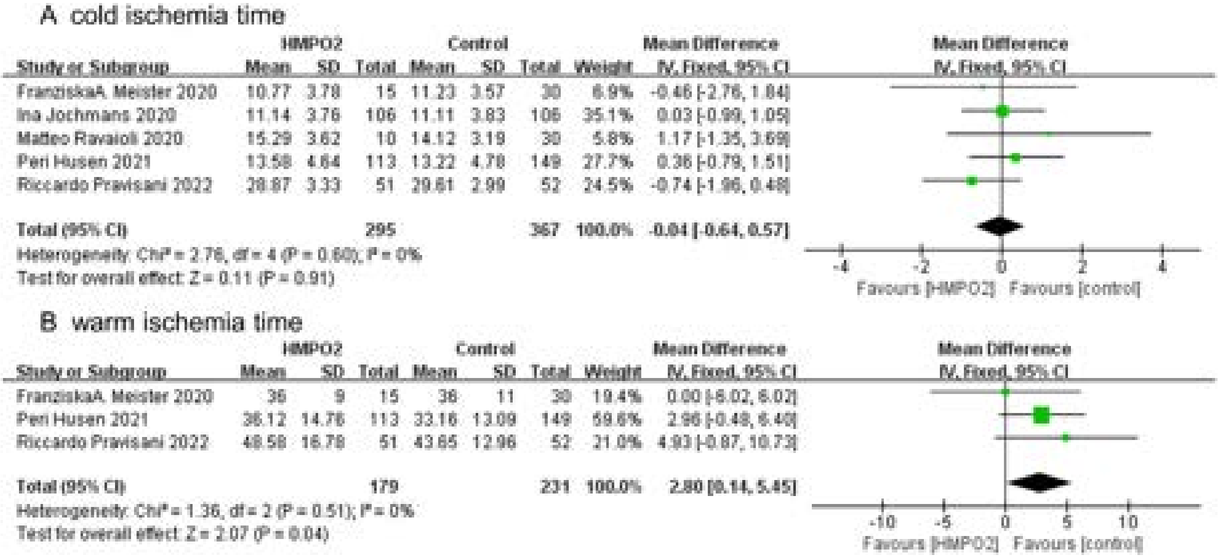
Heterogeneity: Tau² = 10.73; Chi² = 4.10, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 0.68 (P = 0.50)

D 1-year estimated glomerular filtration rate

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ina Jochmans 2020	50.5	19.3	83	46.7	17.1	83	43.3%	3.80 [-1.75, 9.35]
Peri Husen 2021	39.1	14.9	127	40.7	17.8	135	56.7%	-1.60 [-5.57, 2.37]
Total (95% CI)			210			218	100.0%	0.74 [-4.51, 5.98]

Heterogeneity: Tau² = 8.53; Chi² = 2.41, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.28 (P = 0.78)

Fig 7. Forest plot of the impact of $HMPO_2$ on the 7-day (A), 3-month (B), 6-month (C), and 1-year eGFR (D). Compared with the control, $HMPO_2$ has no significant effect on eGFR. eGFR, estimated glomerular filtration rate.



A cold ischemia time

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FranziskaA. Meister 2020	10.77	3.78	15	11.23	3.57	30	6.9%	-0.46 [-2.76, 1.84]
Ina Jochmans 2020	11.14	3.76	106	11.11	3.83	106	35.1%	0.03 [-0.99, 1.05]
Matteo Ravaioli 2020	15.29	3.62	10	14.12	3.19	30	5.8%	1.17 [-1.35, 3.69]
Peri Husen 2021	13.58	4.64	113	13.22	4.78	149	27.7%	0.36 [-0.79, 1.51]
Riccardo Pravisani 2022	28.87	3.33	51	29.61	2.99	52	24.5%	-0.74 [-1.96, 0.48]
Total (95% CI)			295			367	100.0%	-0.04 [-0.64, 0.57]

Heterogeneity: Chi² = 2.76, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)

B warm ischemia time

Study or Subgroup	HMPO2 Mean	HMPO2 SD	HMPO2 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FranziskaA. Meister 2020	36	9	15	36	11	30	19.4%	0.00 [-6.02, 6.02]
Peri Husen 2021	36.12	14.76	113	33.16	13.09	149	59.6%	2.96 [-0.48, 6.40]
Riccardo Pravisani 2022	48.58	16.78	51	43.65	12.96	52	21.0%	4.93 [-0.87, 10.73]
Total (95% CI)			179			231	100.0%	2.80 [0.14, 5.45]

Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)

Fig 8. Forest plot of the impact of $HMPO_2$ on CIT (A) and WIT (B). Compared with the control, $HMPO_2$ shortened graft WIT but had no significant effect on CIT CIT, cold ischemia time; WIT, warm ischemia time.

time of end-HMPO$_2$. Future studies on end-HMPO$_2$ should record the specific start and end times to determine the optimal balance between SCS and HMPO$_2$, maximizing both clinical and economic benefits. Fifth, this study lacked analysis of the composition of the perfusion fluid, which is correlated with organ viability. Analyzing the composition of the perfusion fluid can help us understand the state of the organ and facilitate timely administration of nutrients, extracellular vesicles, and other therapeutic agents to maintain optimal organ conditions. Last, the current research on short-term HMPO$_2$ has mainly focused on the clinical effects of end-point oxygenation, with a lack of relevant research on the application of initial oxygenation in KT. Future studies could investigate this mode of oxygenation.

CONCLUSION

Overall, the application of HMPO$_2$ reduced the number of patients with adverse events and the proportion of severe adverse events. Therefore, we believe that transplant centers should consider using HMPO$_2$ during KT, as discontinuing the use of HMPO$_2$ may deprive transplant patients of the potential benefits of this organ preservation method. Meanwhile, considering factors such as the number of included studies, the sample size of the study subjects, and heterogeneity, it is necessary to conduct RCTs with larger sample sizes to further explore this novel organ storage approach. Given the low cost of supplemental oxygen, the simple extension of HMP has the potential to be rapidly implemented in clinical practice.

AUTHORS CONTRIBUTION

DJ and SG: Conceptualization, investigation, writing - original draft, writing—review and editing, final approval. JL: Data curation, methodology, writing—review and editing, final approval. YZ and HZ: Data curation, writing—review and editing, final approval. SL: Writing - original draft, writing—review and editing, final approval. JL: Supervision, writing—review and editing, final approval.

DATA AVAILABILITY

Data will be made available on request.

DECLARATION OF COMPETING INTEREST

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.transproceed.2025.03.006.

REFERENCES

[1] Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet 2017;390(10105):1888–917.

[2] Rosselli D, Rueda JD, Diaz CE. Cost-effectiveness of kidney transplantation compared with chronic dialysis in end-stage renal disease. Saudi J Kidney Dis Transpl 2015;26(4):733–8.

[3] Ingsathit A, Kamanamool N, Thakkinstian A, Sumethkul V. Survival advantage of kidney transplantation over dialysis in patients with hepatitis C: a systematic review and meta-analysis. Transplantation 2013;95(7):943–8.

[4] Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ. Expanded criteria donors for kidney transplantation. Am J Transplant 2003;3(Suppl 4):114–25.

[5] Campi R, Pecoraro A, Sessa F, Vignolini G, Caroti L, Lazzeri C, et al. Outcomes of kidney transplantation from uncontrolled donors after circulatory death vs. expanded-criteria or standard-criteria donors after brain death at an Italian Academic Center: a prospective observational study. Minerva Urol Nephrol 2023;75(3):329–42.

[6] Hwang JK, Park SC, Kwon KH, Choi BS, Kim JI, Yang CW, et al. Long-term outcomes of kidney transplantation from expanded criteria deceased donors at a single center: comparison with standard criteria deceased donors. Transplant Proc 2014;46(2):431–6.

[7] Suarez-Pierre A, Iguidbashian J, Stuart C, King RW, Cotton J, Carroll AM, et al. Appraisal of donation after circulatory death: how far could we expand the heart donor pool? Ann Thorac Surg 2022;114(3):676–82.

[8] Tingle SJ, Figueiredo RS, Moir JA, Goodfellow M, Thompson ER, Ibrahim IK, et al. Hypothermic machine perfusion is superior to static cold storage in deceased donor kidney transplantation: a meta-analysis. Clin Transplant 2020;34(4):e13814.

[9] Tingle SJ, Figueiredo RS, Moir JA, Goodfellow M, Talbot D, Wilson CH. Machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. Cochrane Database Syst Rev 2019;3(3):Cd011671.

[10] Schlegel A, Porte R, Dutkowski P. Protective mechanisms and current clinical evidence of hypothermic oxygenated machine perfusion (HOPE) in preventing post-transplant cholangiopathy. J Hepatol 2022;76(6):1330–47.

[11] Darius T, Gianello P, Vergauwen M, Mourad N, Buemi A, Meyer MD, et al. The effect on early renal function of various dynamic preservation strategies in a preclinical pig ischemia-reperfusion autotransplant model. Am J Transplant 2019;19(3):752–62.

[12] Patel K, Smith TB, Neil DAH, Thakker A, Tsuchiya Y, Higgs EB, et al. The effects of oxygenation on ex vivo kidneys undergoing hypothermic machine perfusion. Transplantation 2019;103(2):314–22.

[13] Venema LH, Brat A, Moers C, Hart NA, Ploeg RJ, Hannaert P, et al. Effects of oxygen during long-term hypothermic machine perfusion in a porcine model of kidney donation after circulatory death. Transplantation 2019;103(10):2057–64.

[14] Jochmans I, Brat A, Davies L, Hofker HS, Leemkolk FEM, Leuvenink HGD, et al. Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised, double-blind, paired, phase 3 trial. Lancet 2020;396(10263):1653–62.

[15] Husen P, Boffa C, Jochmans I, Krikke C, Davies L, Mazilescu L, et al. Oxygenated end-hypothermic machine perfusion in expanded criteria donor kidney transplant: a randomized clinical trial. JAMA Surg 2021;156(6):517–25.

[16] 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.

[17] Osman KT, Nayfeh T, Alrukby J, Mehta N, Elkhabiry L, Spencer C, et al. Type of donor liver transplant does not affect pregnancy outcomes-a systematic review and meta-analysis. Liver Transpl 2023;29(12):1304–12.

[18] Meister FA, Czigany Z, Rietzler K, Miller H, Reichelt S, Liu WJ, et al. 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.

[19] Pravisani R, Baccarani U, Molinari E, Cherchi V, Bacchetti S, Terrosu G, et al. PO(2) 21% oxygenated hypothermic machine perfusion in kidney transplantation: any clinical benefit? Int J Artif Organs 2022;45(8):666–71.

[20] Ravaioli M, De Pace V, Angeletti A, Comai G, Vasuri F, Baldassarre M, et al. 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.

[21] Casiraghi F, Azzollini N, Todeschini M, Fiori S, Cavinato RA, Cassis P, et al. Complement alternative pathway deficiency in recipients protects kidney allograft from ischemia/reperfusion injury and alloreactive T cell response. Am J Transplant 2017;17(9):2312–25.

[22] Mills EL, Kelly B, O'Neill LAJ. Mitochondria are the powerhouses of immunity. Nat Immunol 2017;18(5):488–98.

[23] Kron P, Schlegel A, Muller X, Gaspert A, Clavien PA, Dutkowski P. Hypothermic oxygenated perfusion: a simple and effective method to modulate the immune response in kidney transplantation. Transplantation 2019;103(5):e128–36.

[24] Lim WH, Chapman JR, Coates PT, Lewis JR, Russ GR, Watson N, et al. HLA-DQ mismatches and rejection in kidney transplant recipients. Clin J Am Soc Nephrol 2016;11(5):875–83.

[25] Lefaucheur C, Gosset C, Rabant M, Viglietti D, Verine J, Aubert O, et al. T cell-mediated rejection is a major determinant of inflammation in scarred areas in kidney allografts. Am J Transplant 2018;18(2):377–90.

[26] Cippà PE, Liu J, Sun B, Kumar S, Naesens M, McMahon AP. A late B lymphocyte action in dysfunctional tissue repair following kidney injury and transplantation. Nature Communications 2019;10 (1):1157.

[27] Shaw PE, Bohmann D, Sergeant A. The SV40 enhancer influences viral late transcription in vitro and in vivo but not on replicating templates. Embo j 1985;4(12):3247–52.

[28] Horné F, Drefs M, Schirren MJ, Koch DT, Cepele G, Jacobi SJ, et al. Hypothermic oxygenated machine perfusion (HOPE) prior to liver transplantation mitigates post-reperfusion syndrome and perioperative electrolyte shifts. J Clin Med 2022;11(24).

[29] Trotter PB, Jochmans I, Hulme W, Robb M, Watson C, Neuberger J, et al. Transplantation of kidneys from DCD and DBD donors who died after ligature asphyxiation: the UK experience. Am J Transplant 2018;18(11):2739–51.

[30] Heylen L, Jochmans I, Samuel U, Tieken I, Naesens M, Pirenne J, et al. The duration of asystolic ischemia determines the risk of graft failure after circulatory-dead donor kidney transplantation: A eurotransplant cohort study. Am J Transplant 2018;18(4):881–9.

[31] Gallinat A, Efferz P, Paul A, Minor T. One or 4 h of "in-house" reconditioning by machine perfusion after cold storage improve reperfusion parameters in porcine kidneys. Transpl Int 2014;27 (11):1214–9.

[32] Hosgood SA, Mohamed IH, Bagul A, Nicholson ML. Hypothermic machine perfusion after static cold storage does not improve the preservation condition in an experimental porcine kidney model. Br J Surg 2011;98(7):943–50.

[33] Darius T, Vergauwen M, Smith TB, Patel K, Craps J, Joris V, et al. Influence of different partial pressures of oxygen during continuous hypothermic machine perfusion in a pig kidney ischemia-reperfusion autotransplant model. Transplantation 2020;104(4):731–43.