Trabajo Fin de Grado

Grado en Medicina

Pulsatile Preservation in Kidney Transplantation: Strengths, limitations and future directions

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1. INTRODUCTION

1.1. RESEARCH QUESTION AND PROBLEM FORMATION

Spain is well known for its altruism when it comes to transplants. The National Transplant Organisation states the number of kidney transplants in around 3000 per year nationwide [1] **(Figure 1)**. This high amount of donation makes it much more likely for a patient in end-stage renal disease to get the treatment needed for curing the disease: a new kidney.

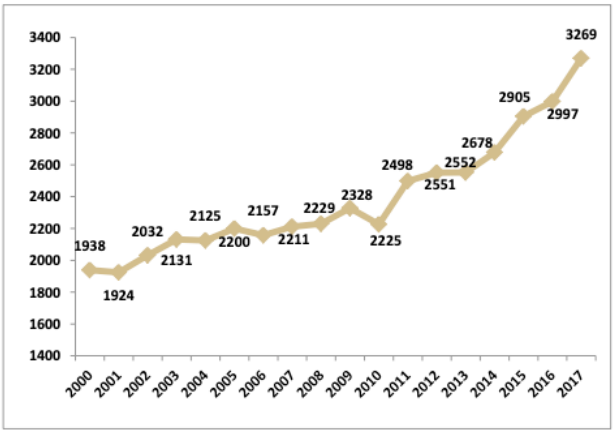

Figure 1: Number of kidney transplants in Spain from 2000 to 2017[1]

Although there are higher chances of getting access to a donor kidney, kidney disease's incidence is increasing rapidly as the life expectancy of the population increments. Thus, physicians are working to span the criteria for an organ to be considered adequate for donation: Expanded Criteria Donor (EDC).[2,3,4]

For considering those organ suitable for donation, the storage and maintenance in between the extraction and the placement is key. Static cold storage (CS) is generally used to preserve donor kidneys until its placement in the recipient. However, few studies in the latest 15 years have addressed the possibility of a perfusion machine with continuous hypothermic perfusion to maintain the organ in perfect preservation during the time of cold ischemia.

This systematic review aims to go through the existent data on hypothermic machine perfusion (HMP) up to the date to address this possibility.

1.2. BASICS ON CHRONIC KIDNEY INSUFFICIENCY

Renal transplantation is the final solution to a variety of diseases leading to chronic terminal kidney insufficiency.

1.2.1. Chronic terminal kidney insufficiency: definition, grades, causes, symptoms, diagnosis and treatments.

Chronic terminal kidney insufficiency, also called end-stage renal disease, occurs when chronic kidney reaches an advanced state. In this situation, the kidneys are no longer able to work as they should to meet the body's needs. [6,7,8]

Kidneys main function is to filter wastes and excess fluids from the blood, which are then excreted through urine. When kidneys lose their filtering capabilities, dangerous levels of fluid, electrolytes and wastes can build up in the body.

1.2.1.1. Stages

Kidneys decrease their capacity gradually. This characteristic allows us to classify the disease into five different stages of kidney insufficiency **(Table 1).** To determine the stage of kidney disease, we perform a blood test to check the glomerular filtration rate (GFR). The GFR provides us with an approximate measure of how much blood the kidneys filter each minute according to the clearance of creatinine, recorded as millilitres per minute (mL/min). As the GFR declines, so does the kidney function.

When the person’s kidneys cannot at a level that's necessary for day-to-day life, we say that the patient is at end-stage renal disease. End-stage renal disease usually occurs when kidney function is less than 10 percent of normal.

Table 1. Stages for kidney disease.

Kidney disease stage	GFR, mL/min	Kidney function
American National Kidney Foundation		
Stage 1	90 or above	Normal or near-normal kidney function + symptoms *
Stage 2	60 to 89	Mild loss of kidney function + symptoms *
Stage 3a	45 to 59	Mild to moderate loss of kidney function
Stage 3b	30 to 44	Moderate to severe loss of kidney function
Stage 4	15 to 29	Severe loss of kidney function
Stage 5	Less than 15	Kidney failure

GFR: glomerular filtration rate

*A GFR between 60 and 120 without any symptoms related to renal failure is not considered chronic renal disease. A GFR below 60, with or without associated symptoms will be considered chronic renal disease.

1.2.1.2. Causes

There are multiple conditions that can impair kidney function leading to kidney damage that can worsen over several months or years. The most common diseases[5] that can generate function lose are:

- Type 1 or type 2 diabetes
- High blood pressure
- Glomerulonephritis (inflammation of the kidney's filtering units or glomeruli)
- Interstitial nephritis (an inflammation of the kidney's tubules and surrounding structures)

- Polycystic kidney disease
- Prolonged obstruction of the urinary tract, from conditions such as enlarged prostate, kidney stones and some cancers
- Vesicoureteral reflux
- Recurrent pyelonephritis (kidney infection)

1.2.1.3. Symptoms

When kidneys start decreasing their function the appearance of symptoms may vary in each patient. Some show early symptoms with little decrease of the GFR, while other kidneys are highly adaptable and able to compensate for lost function and because of it the patient won't show any until progressed end-stage renal disease. Early in chronic kidney disease, you may have no signs or symptoms. Signs and symptoms might include:

- Nausea
- Vomiting
- Loss of appetite
- Fatigue and weakness
- Sleep problems
- Changes in how much you urinate
- Decreased mental sharpness
- Muscle twitches and cramps
- Swelling of feet and ankles
- Persistent itching
- Chest pain, if fluid builds up around the lining of the heart

- Shortness of breath, if fluid builds up in the lungs
- High blood pressure (hypertension) that's difficult to control

However, these signs and symptoms are very nonspecific, meaning they can also be caused by other illnesses.

1.2.1.4. Diagnosis

In consequence to the inconstancy of signs and symptoms, diagnosis of renal disease may result difficult. Often patients suffering from diseases known for causing kidney damage are tested for it. Tests and exams to detect end-stage renal disease may include:

- **A discussion of your health history,** including personal and family health history.
- **A physical exam,** including height, weight and blood pressure. We must also looks for signs of heart or blood vessels problems and a neurological exam.
- **Blood tests,** to measure the amount of waste products, such as creatinine and urea, in the blood.
- **Urine tests,** to check the level of the protein albumin in your urine, as a high albumin level may indicate kidney disease.
- **Imaging tests,** such as ultrasound, magnetic resonance imaging or a computed tomography scan, to assess kidneys' structure and size and look for morphological abnormalities.
- **Taking a sample of kidney tissue (biopsy),** to examine under a microscope to learn what type of kidney disease and how much damage there is.

These tests may be repeated over time to follow the progress of kidney disease.

1.2.1.5. Treatment

At early stages of chronic kidney disease, the main focus of treatment is the cause of that damage (controlling sugar blood levels, blood pressure…). When the damage increases up to end-stage renal disease, treatment may include: dialysis and/or kidney transplant.

Dialysis is a procedure in which a filter different from the filters in the kidney takes over kidneys' function. The dialysis filter removes extra fluids and waste products from blood, restoring electrolyte levels, and helping control of the blood pressure. There are several methods of dialysis, being the most common ones peritoneal dialysis and hemodialysis. [9]

- **Peritoneal dialysis**

During peritoneal dialysis, the filters used are in the same patient's abdomen. Blood vessels in the abdominal lining called peritoneum fill in for the kidneys with the help of a fluid that washes in and out of the peritoneal space. Peritoneal dialysis' main benefit is that it can be done at home, so the patients won't need to stay for long hours at a hospital.

- **Hemodialysis**

In the so-called hemodialysis, a machine does the work of filtering harmful wastes, salts and fluid from your blood. The disadvantage of hemodialysis is the long hours spent in medical facilities as it is rarely done at the place of residence

However, dialysis is not a definitive solution. The only permanent solution would be transplantation of a healthy kidney.

1.2.2. Kidney transplantation:

Kidney transplant is the surgical procedure to place a healthy kidney from donor into a person whose kidneys no longer function properly. This procedure is often the treatment of choice for kidney failure compared to a lifetime on dialysis. The indication for kidney transplantation is to have a chronic terminal kidney insufficiency stage V or end-stage renal disease.

Kidney transplantation have benefits in comparison to dialysis, as the procedure imply a better quality of life, lower death risk, fewer dietary restriction and overall lower treatment cost.

Unfortunately, for certain people with kidney failure, a kidney transplant may be more risky than dialysis. There are certain conditions that may prevent the patients from being eligible for a kidney transplant, such as advanced age, severe heart disease, active or recently treated cancer, dementia, alcohol or drug abuse or any other factor that could affect their ability to safely undergo the procedure and take the medications needed to prevent organ rejection.

Also, for treating end-stage kidney disease, one donated kidney is needed to replace two failed kidneys. This fact makes living-donor kidney transplantation an option, as one kidney would be enough for the donor to survive and could replace the function of the two failed kidneys in the recipient.

If a compatible living donor isn't available, the patient may be placed on a kidney transplant waiting list to receive a kidney from a deceased donor.

1.2.2.1. Types

Therefore, we could classify the types of kidney transplantation into two main groups: living donor kidney and deceased-donor transplant.

- **Living-donor kidney transplant**

As mentioned, only one healthy kidney is needed to replace two non-functioning kidneys, making living-donor kidney a possibility. [10] The donor would also live with one healthy kidney, enough to cover all functions. In comparison with deceased-donor kidney transplant, there are several benefits:

- Less or no time on a waiting list, as donors are usually people known by the patient
- Better short- and long-term survival rates

- The possibility to schedule the transplant. Decease-donor transplantations are usually conducted as an emergency procedure.
- Living-donor kidneys have a lower rate of delayed graft function (DGF).

Other risks of every transplant (associated with the surgery, organ rejection and side effects of anti-rejection medications) are similar in both types.

- **Deceased-donor kidney transplant:**

Deceased-donor kidney transplant is when a kidney from a recently deceased person is removed and placed in a recipient who is in need of transplantation.

Inside this classification we can split the donors into donors after brain death (DBD) and donors after circulatory death (DCD), which could also be named asystolic donors or non-heart-beating donors (NHBD).

Deeper in this last subcategory, we find the Maastricht classification **(Table 2)** of donors after circulatory death, first stated in the nineties, which was agreed as the growing experience in DCD led up to the need to distinguish several categories of potential donor in different end‑of‑life situations.

It's useful as it is able to characterize the different DCD situations and the different categories of donors, considering technical and medical aspects (such as organ viability, preservation modalities or graft survival) and ethical aspects. Attempts to improve the Maastricht classification have focused on adding more categories, with the objective of distinguishing the different ischaemic insults to the organ and consequently different outcomes, but many attempts have not settled in, as one of the reasons Maastricht is used is its simplicity and usefulness. Only the modified Maastricht classification of DCD done in Paris in 2013 **(Table 3)** has seemed to solidify as it kept intact the simplicity of the original classification.

Table 2. Maastricht classification of donors after circulatory death.

Category	Description	Control
I	Dead on arrival	Uncontrolled
II	Unsuccessful resucitation	Uncontrolled
III	Awaiting cardiac arrest	Controlled
IV	Cardiac arrest while brain dead	Uncontrolled

Table 3. The Modified Maastricht Classification of DCD

<table>
<tr><th colspan="2">Category</th><th>Situation</th><th>Description</th></tr>
<tr><td colspan="2">I</td><td rowspan="3">Found dead</td><td rowspan="3">Sudden unexpected CA without any attempt of resuscitation by a life-medical team; WIT to be considered according to National life-recommendations in place; reference to in- or out-of-hospital life-setting</td></tr>
<tr><td>IA</td><td>Out of hospital</td></tr>
<tr><td>IB</td><td>In hospital</td></tr>
<tr><td colspan="2">II</td><td rowspan="3">Witnessed cardiac arrest</td><td rowspan="3">Sudden unexpected irreversible CA with unsuccessful resuscitation life-by a life-medical team; reference to in or out of hospital life-setting</td></tr>
<tr><td>IIA</td><td>Out of hospital</td></tr>
<tr><td>IIB</td><td>In hospital</td></tr>
<tr><td colspan="2">III</td><td>Withdrawal of life-sustaining therapy</td><td>Planned withdrawal of life-sustaining therapy*</td></tr>
</table>

IV	Cardiac arrest while life-brain dead	Sudden CA after brain death diagnosis during donor life-management but prior to planes organ recovery.

CA= circulatory arrest.

* This category mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically assisted CA, expected CA) and organ donation described as the fifth category.

Category I

Dead on arrival includes victims who arrive to the hospitals after accidents that have not been resuscitated (for clear reasons of death). These deceased patients could arrive to the emergency department and become a donor if the organs are deemed appropriate for donation. The main criterion for acceptance for donation is warm ischemia time (WIT), which is the time between the circulatory arrest and the start of the cooling. This time should be of less than 45 min to consider the organs adequate for donation. Due to the commonly uncertain duration of WIT, there are few examples of successful organ donation in this category.

Category II

Unsuccessful resuscitation is a category that includes patients brought to the emergency room while being resuscitated. If the cardiopulmonary resuscitation (CPR) is unsuccessful, the patient would be declared dead. According to the Maastricht classification, a period of "no-touch" after cardio-circulatory arrest (CA) to ensure a situation equivalent to brain death. If the deceased patient is a donor, the hospital crew can immediately proceed to the cooling preservation,

Timing in the uncontrolled DCD process.

1. No flow: Kidney ≤30 min; Liver ≤ 15 min

2. CPR duration: ≥30 min
3. No-touch period: 2 min to 20 min
4. Total WIT: 120 min to 150 min

In some countries, which include Spain, two subcategories were added in the Paris 2013 reformulation due to different logistic conditions according to the site where CA occurs: IIa for out-of-hospital and IIb for in-hospital. However, most of this cases occur out of the hospital, so this further classification is not always used.

Category III

Awaiting cardiac or circulatory death includes patients whose circulatory death occurs after withdrawal of life-sustaining therapies (WLST), previously planned and agreed with patient and/or families. That's why we consider it a controlled situation, as the fact that the CA is planned allows the medical practitioners to shorter as much as possible the ischemia time, which is very beneficial for all organs to be donated.

Timing of the controlled DCD process.

1. Functional WIT starts when SBP is ≤ 50 mmHg or ≤ 60 mmHg
2. No-touch period: 2 min to 20 min

Category IV

Cardiac arrest in a brain-dead donor is a category that includes patients diagnosed with brain death who suffer an unexpected arrest before the planned organ recovery. Firstly, medical practitioners should try to maintain the organ circulation and perfusion but in case of failure, the patient would be included in the category IIb (uncontrolled CA inside the hospital).

1.3. THEORETICAL FRAMEWORK ON THE HYPOTHERMIC PERFUSION MACHINE

1.3.1. Kidney preservation and storage

The donated kidney can be transported stored on ice or connected to a machine that provides oxygen and nutrients until the kidney is transplanted into the recipient. The problem with cold storage (CS) is that long periods of cold ischemia are strongly associated with delayed graft function (DGF). As DGF is linked to lower graft survival, perfusion machines were designed to deliver nutrients, substrates and remove toxic waste products during that time.

This machine pumps continuously cold preservation solutions through the renal artery to the kidneys. In Europe, there are two different devices commercialised:

Two different devices are currently commercially available in Europe: LifePort Kidney Transporter and RM3. However, LifePort is the only machine that allows transportation commercialised in Europe up to date.

1.3.1.1. LifePort Kidney Transporter [12]

The machine keeps the kidney in a bath of preservation solution surrounded by an ice box. Every use of the machine requires different perfusion kits, which are specific consumables and preservation solutions to each device **(**see **Figure 2)**.

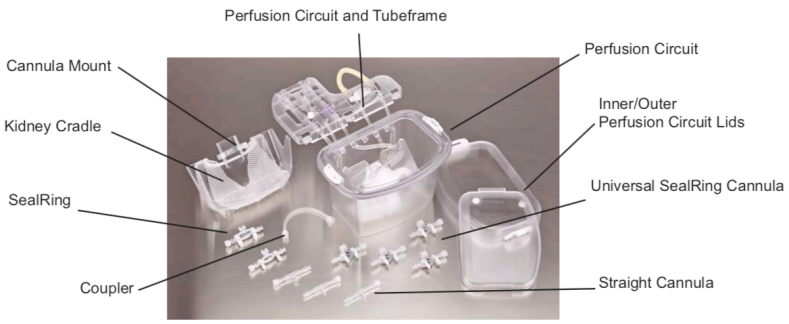

Figure 2: LifePort Kidney Transporter perfusion kit

The solution is withdrawn from the reservoir and pumped through the renal artery. It can also monitor several values which could potentially be of use to assess graft quality[11]: resistive index, temperature, pressure and flow dynamics.**(**see **Figure 3)**.

Figure 3: LifePort Kidney Transporter

The procedure is simple. After the extraction of the kidney, the following steps must be taken for cannulisation of the kidney:

1. Place both the kidney and the proper cannula into the sterile field. Multiple cannulas are available, depending on the characteristics.
2. Open the cannula.

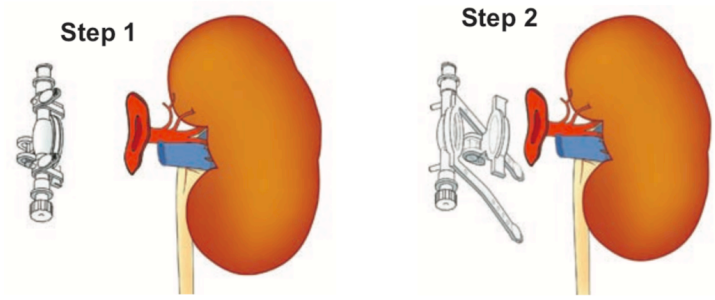

Figure 4.1: Opening the cannula.

3. Insert the aortic patch through the cannula ring.
4. Ensure the patch covers the entire sealing ring.

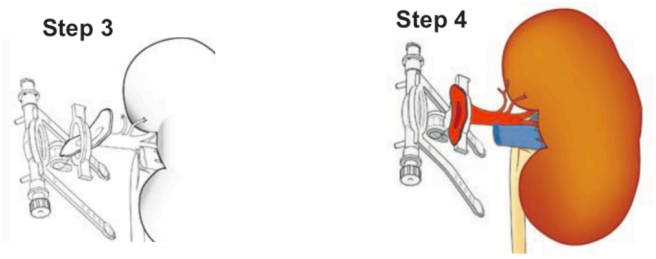

Figure 4.2: Insertation of aortic patch through cannula ring

5. Close the cannula, securing the tissue between the two halves.
6. Secure the cannula by wrapping the two straps and fix them to their posts.

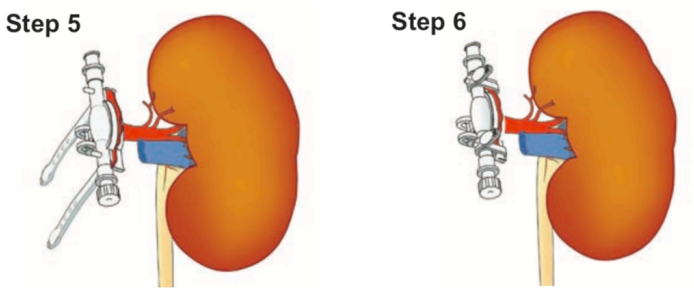

Figure 4.3: Closing and sealing of aortic patch

7. Make a small flow of solution through the cannula to ensure there are no leaks. Correct if there are.
8. Place the kidney in the machine and snap the cannula into the correct position.

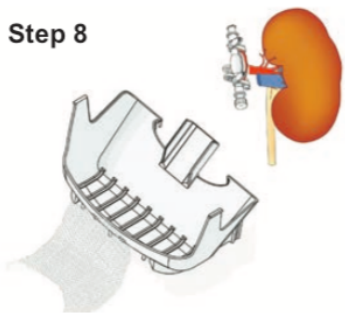

Figure 4.4: Placing of kidney in machine

9. Adjust the height and rotation of the cannula to the correct position the vessel.
10. Ensure there are no twists or occlusions in the vessel.
11. Secure the organ by adjusting the net.

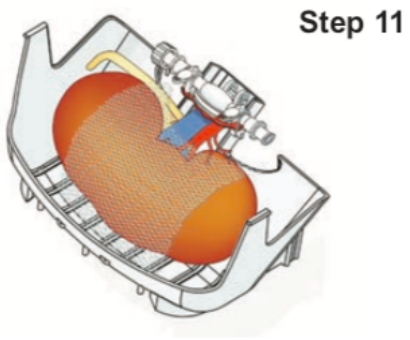

Figure 4.5: Securing kidney in machine

After cannulisation, the kidney should be secured in the machine and connected to the solution flow as shown in the **Figure 5**.

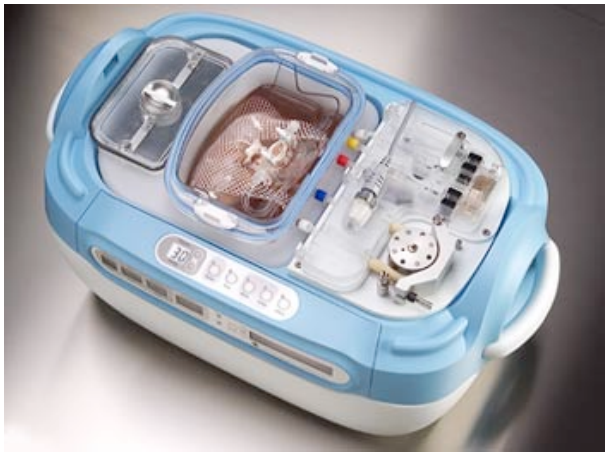

Figure 5: Kidney properly placed in LifePort Transporter

Once properly placed, the machine will provide the parameters of study: pressure, flow, resistance and temperature. Continuous perfusion is thought to decrease the vascular resistance and increment the flow into the organ, as the constant flow acts as a vasodilator. The operator will settle the systolic pressure, and it may be lower than

the established but never higher. Finally, the temperature will be lowered by placing ice into the ice container, maintaining at all times a temperature between 0º and 4ºC.

2. OBJECTIVES.

The objective of the present study is to analyse advantages of hypothermic machine perfusion and its usefulness in comparison to cold storage, focusing on the following items:

The final outcome of a transplant is the general survival of the organ in the recipient. Thus one of the main areas of focus will be the comparison of global graft survival (GS) in cold storage versus hypothermic machine perfusion and the indications of the HMP over CS.

Furthermore, other interesting area to work in is the time in between the placement of the kidney and the time it starts working properly. After the transplant, patients usually have to undergo dialysis for an inconstant period of time. A contrast between the delayed graft function (DGF) in kidneys stored in ice versus those in hypothermic perfusion in the latest studies will be conducted.

There are also economic differences among cold storage and hypothermic perfusion. Analysis of the overall efficiency will be aimed, as it is crucial for a transplantation program financed publicly as Spain is.

Finally, the monitoring of the graft's constants is being studied in order to determine if that information is enough to consider an organ valid for transplantation, substituting current analysis such as a biopsy.

To sum up, the main objectives of this study are:

1. Cold ischemia versus hypothermic machine perfusion in global graft survival and delayed graft function.
2. Renal resistance as an indicator of graft quality. Prognostic value of graft monitoring.
3. Economic impact of the introduction of the hypothermic machine perfusion in the kidney transplant programs.

3. METHODS.

This study is a systematic review of the scientific information about the current data on hypothermic machine perfusion. The main source of information was medical databases, where a search for systematic reviews and clinical trials was made. The search aimed to obtain actual, complete, wide information in order to be able to answer concrete objectives previously established.

Initially, several basic researches were made on Pubmed and/or UpToDate for the terms “Chronic terminal kidney insufficiency”, “ Kidney transplant”, “Maastricht classification” and “Kidney donation”. This preliminary search also included LifePort Kidney Transporter Operator’s Manual for further information on the theoretical background of the hypothermic machine perfusion.

Thereafter, a research was conducted for the articles to be included in the review. A primary examination was made under the search on Pubmed of “hypothermic machine perfusion”, including free full text articles publish in the last 10 years. The inclusion of “AND kidney” and specification of humans articles were necessary, as many of the results were based on animals and/or liver perfusion. From the 25 studies, only 11 were included as the rest studied other data not associated with the objectives settled.

Further research included Ovid database, which provided access to Embase and Medline resources. Again, full texts were searched, and older articles were included to analyse the progress on the machine. Under the name “delayed graft function AND hypothermic kidney machine perfusion”, human, full text in both English and Spanish was searched, leading to 29 studies, 20 of which were included on this review.

To tackle the objective of the machine being able to replace other methods of assessing kidney graft quality, a search in Ovid database was made involving the search “hypothermic machine perfusion kidney quality” and also “hypothermic kidney machine perfusion prognosis” in humans. Out of this search, 4 articles were included in the review.

Finally, for the economic search, same procedural was followed for "hypothermic kidney machine perfusion economic". 11 articles were included as many only involved the cost of the procedure in a determined centre.

To sum up, the final number of 44 studies were incorporated to the review, including general articles, studies focused in global graft survival and delayed graft function, evaluations of the machine to assess kidney graft quality and economic studies.

4. OUTCOMES:

4.1. COLD ISCHEMIA VERSUS HYPOTHERMIC MACHINE PERFUSION IN GLOBAL GRAFT SURVIVAL AND DELAYED GRAFT FUNCTION.

The analysis of outcomes regarding global graft survival and delayed graft function includes several clinical trials, observational studies and also 4 systematic reviews on the subject. Lower delayed graft function was thought to increase the global graft survival, leading to study if such assumption was based on evidence.

Several articles included a difference between dead after cardiac arrest (DCD) and expanded criteria donors (ECD) versus donors after brain dead (DBD). Such specifications vary, and some studies obtained different outcomes depending on the donor type.

Moers et al.[13] followed 336 international donors for a year. Each donor had one kidney maintained in cold ischemia and the other in hypothermic machine perfusion. The study assumed that allografts from donors after cardiocirculatory death are known to have higher rates of delayed graft function.[14, 15] The use of such grafts is increasing in most countries and so methods to decrease DGF should be studied. They observed that out of the 336 followed patients; delayed graft function was developed in 70 patients in the machine-perfusion group versus 89 in the cold storage group. As for one-year graft survival, it was superior in the machine perfusion group (94% vs 90%, p=0.04). Therefore, they concluded that machine perfusion could be considered to have a beneficial effect on the short-term outcome in all common types of deceased-donor kidney transplantation.

Patel et al. [16] decided to study the reduction in DGF rates specially focusing on donors after cardiac arrest, as HMP is known to be decrease DGF in all kinds of donors. [14, 17,18,19] Basing on that information, they assume that the DCD group would benefit from the HMP the most and so the study aims to review the outcomes for DCD kidneys in CS versus HMP. A multicentre observational study was conducted, in which 4529 kidneys were storage in cold and 864 were placed in the perfusion machine during 8 years (January 2007- December 2015). Their overall conclusion for delayed graft function was a considerable decrease on the machine perfusion group (34.2% versus 42%, p= 0.001), which concurs with the known data. However, in the analysis of the global graft survival there is no significant evidence of an association between preserving the kidneys in CS or HMP (p= 0.452), meaning that even if the delayed graft function is lower using the machine there are no proven difference in the global survival.

Gallinat et al. [20] assume the evidence stating that delayed graft function is lower and global graft survival is increased given by Moers et al. [13] However, they consider insufficient the evidence on expanded criteria donors, so they aim to study those differences in their centre during 3 years. They studied 43 expanded criteria patients whose kidneys were one preserved in cold ischemia and the other attached to the hypothermic machine perfusion. Included donors were between 60 and 82 years. Out of the 43 pairs of ECD studied, delayed graft function was significantly lower in the HMP group (11.6% versus 20.9%, p=0.024). The study showed that regarding global graft survival there is, as shown in **Figure 5,** a tendency toward improved graft survival in HMP although it has not reached significance.

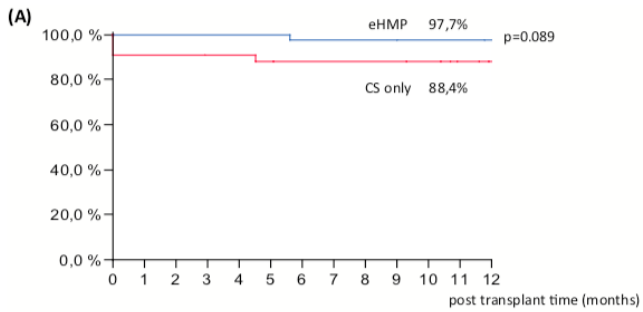

Figure 5. Gallinat et al. Global Graft Survival in Machine Perfusion Group versus Cold Storage Group

Additional studies show precisely the evidence in the difference in the delayed graft function depending on the storage of the graft. As shown in **Table 4,** outcomes from several studies point that there is a significant decrease on the machine perfusion group regarding DGF. However, studies on graft survival do not reach the statistical signification, showing in **Table 5** nothing more than a tendency towards improvement of the global graft survival in machine perfusion group.

Table 4. Delayed Graft Function in Machine Perfusion Group versus Cold Storage Group in latest studies.

Main author, year	Sample size	DGF in Machine Perfusion Group	DGF in Cold Storage Group	P Value
Moers et al. 2009 [13]	336 pairs 672 transplants	20.8 %	26.5%	0.01
Patel et al., 2018 [16]	4529 in CS 864 in MP	34.2%	42%	0.001
Gallinat et al., 2016 [20]	43 pairs 86 transplants	11.6%	20.9%	0.024
Jochmans et al., 2010 [17]	164	53.7%	69.5%	0.025
Treckmann et al., 2010 [21]	82 pairs 164 transplants	22%	29.7%	0.047
Matsuoka et al., 2006 [22]	139	26%	37%	0.001

Table 5. Graft Survival in Machine Perfusion Group versus Cold Storage Group in latest studies.

Main author, year	Sample size	Graft Survival in Machine Perfusion Group	Graft Survival in Cold Storage Group	P Value
Moers et al. 2009 [13]	94	94 %	90%	0.04

Patel et al., 2018 [16]	4529 in CS 864 in MP	-	-	0.452
Gallinat et al., 2016 [20]	43	97.7%	88.4%	0.089
Jochmans et al., 2010 [17]	164	95.1%	93.9.%	0.062
Treckmann et al., 2010 [21]	82 pairs 164 transplants	92.3%	80.7%	0.164
Matsuoka et al., 2006 [22]	139	-	-	0.49

4.2. RENAL RESISTANCE AS AN INDICATOR OF GRAFT QUALITY. PROGNOSTIC VALUE OF GRAFT MONITORING.

The hypothermic perfusion machine enables the operator to monitor several indicators; more specifically LifePort kidney transportation machine shows temperature, flow, pressure and resistance. No evidence has been proven regarding temperature, flow and pressure. Resistance index has however proven to be a good early indicator for delayed graft function or low glomerular filtration rate.

Jochman et al. [23] considered that even if vascular renal resistance (RR) during hypothermic machine perfusion is frequently used as an indicator of graft quality; such association has not been validated. Thus, the study collected RR values of 302 kidneys maintained in the hypothermic machine perfusion and studied the association between RR and delayed graft function and 1-year graft survival. After the study, they concluded that a RR could be use as an additional parameter to assess the graft. RR values over 0.3 mmHg/mL/min were proven to be associated with 1-year graft failure. Overall, they concluded that RR is an independent risk factor for the development of DGF and 1-year graft failure, not useful as a stand-alone assessment as more parameters are needed to achieve needed accuracy.

Sandal et at.[24] conducted a retrospective cohort study during 5 years. After studying 274 kidney transplants, they reach a similar outcome. Kidneys with higher RR tended to had a lower glomerular filtration rate than those with a lower RR (102.72 ±

27.51 versus 94.49 ±30.36, p = 0.01). Taken together all their findings, the summarize stating that RR is an independent predictor of long graft survival. Out of the studies regarding RR as a prognostic factor, the one conducted by Sandal et al. provides the longest follow-up to date when it comes to studies using LifePort machines.

Different studies evaluating transplants by parameters of the LifePort machine have tried to conclude on a renal resistance threshold during hypothermic machine perfusion. These results are shown in **Table 6** with the general outcome of the study.

Table 6. Evaluation of RR as a prognosis parameter in studies using LifePort machine.

Main author, year	Threshold (mmHg/mL/min)	Sample size	Follow up	Outcome
Sandal et al. 2018 [24]	0.4 and 0.2	274	5 years	RR during HMP is associated with lower GFR
Burgos Revilla et al. 2015 [29]	0.3 and 0.4	90	1 year	RR is not predictive of graft survival
Yushkov et al. 2012 [30]	<0.2, 0.2-0.3, >0.3	454	1 year	RR>0.3 is predictive of 1-year graft survival
Jochmans et al. 2011 [23]	None	336	1 year	Terminal RR predictive of graft failure

Gelpi et al [31], an independent study using only DCD kidney transplant stated a precise threshold for RR. A total of 194 transplants were included and the factor to study was a glomerular filtration rate lower than 30 mL/min at 6 months after transplantation. They concluded that for RR over 0.3 there was a 2.16 higher rate of GFR lower than 30mL/min in the group of recipient under 60 years, comparing to an almost 18 higher rate in the recipients over 60.

4.3. ECONOMIC IMPACT OF THE INTRODUCTION OF THE HYPOTHERMIC MACHINE PERFUSION IN THE KIDNEY TRANSPLANT PROGRAMS.

Multiple studies have proven the benefits of hypothermic machine perfusion in avoiding or shortening delayed graft function and the potential of monitoring parameters such as pressure or renal resistance. With all the evidence in favour of the perfusion machine, next step to the introduction in the transplant programs is to assess the costs and to perform cost-efficiency studies. Although 11 studies were included and reviewed, only results from Gomez et al. are shown in this report, as it is the only study based on the Spanish public transplant program.

Gomez et al. [42] assumes that MP could be the standard procedure for kidney transplantation in expanded criteria donors one day, and however, machine perfusion remains way more expensive than cold storage. Thus, they aim to study a cost-effectiveness analysis, to estimate the economic impact of incorporating the LifePort machine into the hospital policy of extended criteria donors.

They compared prospective costs estimation depending on the diagnosis-related group the recipients is included in and the possible outcomes of the transplant. Different outcomes included the possibility of delayed graft function and primary non-function, factors that would increase the cost of the transplant as the patients would stay for a longer period in the hospital and require dialysis. Unit costs used to calculate the treatment costs are included in **Table 7.**

Table 7. Direct Medical Costs and Prices based on Diagnosis-Related Groups[42]

Human resources	$1,035
Hospital stay per day	$186
Intermediate care unit stay per day	$1,450
Hemodialysis per treatment (in-hospital)	$328
Kidney biopsy	$397
Immunosuppression	$3,027
Graft removal (nephrectomy)	$7,336
Preservation: MP	
Number of machines	2
Transplant per year	40
Costs per transplant	$58
Disposables (including fluids)	$1,337
Total costs MP preservation per transplant	$1,395
Preservation: CS	
Preservation fluids	$165
Disposables	$20
Total costs CS preservation per transplant	$185

Prices in US dollars.
MP, machine perfusion; CS, cold storage.

In the outcome analysis factors that would mean a higher final price such as hospital stay, dialysis needed and resource consumption were assessed and included in **Table 8.**

Table 8. Differences Between Expected Costs for MP and CS[42]

Donor type	Brain-dead donors (ECD)
ECD (proportion)	55.7% (34/61)
Donor age (y), mean (SD)	72.9 (SD 7.3)
Hospital stay (d), median (IQR)	
IGF	10 (IQR 16)
DGF	13 (IQR 9)
PNF	55 (IQR −)
Hemodialysis (sessions), median (IQR)	
IGF	0 (IQR 0)
DGF	1 (IQR 3)
PNF	18 (IQR −)
Biopsy (number), median (IQR)	
IGF	0 (IQR 0)
DGF	0 (IQR 0)
PNF	1.5 (IQR −)

ECD, expanded criteria donors; SD, standard deviation; IQR, interquartile range; IGF, initial graft function; DGF, delayed graft function; PNF, primary nonfunction.

All in all the study showed than even if the initial costs of machine perfusion are hhigher than cold storage, there overall analysis estimates than MP would actually save an average of $505 in comparison to CS. In this scenario, they conclude than MP technology is cost-effective in kidney transplantation program for extended criteria donors.

5. CONCLUSION

This systematic review sought to assess different aspects of the use of hypothermic machine perfusion versus the widely extended use of cold storage. Although the review was statistically significant in some points, much more research is needed in order to state most of the issues.

Regarding hypothermic machine perfusion as a tool to reduce the frequency of delayed graft function as well as its duration there is clinical evidence that support this hypothesis. Deeper in this theory, it is now known that the grafts that would most benefit from the use of HMP are those extended criteria donor grafts, as these grafts present the highest rate of delayed graft function.

However, looking closer to the global graft survival we might deduct that if delayed graft function is one of the main cause of global graft survival, reducing such cause would immediately reduce the quota of graft failure. Although evidence does show a tendency towards that idea, there is not yet enough clinical experience and research on the topic so as to reach the statistical significance.

Moving forward, while reviewing the published work on the different parameters to assess graft quality little literature was found. Nevertheless we can come to the conclusion that when giving graft prognosis renal resistance constitutes a very useful parameter to include among others, but should not be used as a stand alone criteria. As for the precise parameter, evidence points at a resistance not higher than 0.3 mmHg/mL/min to predict the most optimal transplant results.

Final point assessed, the economic impact of the implementation of machine perfusion in transplant programs. This area is considerably the one most research is needed, as literature so far include different costs for each centre, with different politics on the topic and thus are subject to the location of the study.

Overall several difficulties were found while reviewing this area:

- There is a lack of enough clinical evidence in our country, based primarily to the scarcity of personnel to gather data and the low habit to use the machine, as it requires longer preparation and qualification not all workers possess.
- Although systematic reviews do exists, the literature to review is limited and so not many studies are included. Longest review in literature, San Miguel et al.[43] includes 9 clinical and is primarily focused in Belgian kidney transplantation program.
- Evidence found is restricted to specialised centres with high experience on the subject. Thus, it is difficult to overlap to smaller clinical centres with lower to none experience.
- There is a lack of longer follow up of transplants after using HMP. Longest study (Sandal et al. [24]) followed up for just 5 years after transplantation.

- Before the year 2000 all the studies were made based on machines different to LifePort, which showed no monitoring and/or were not able to be transported.

As a final result, the conclusions are consistent with most of the published data on the subject, which is undoubtedly not consistent enough to state whether the use of the hypothermic machine perfusion is evidence-based indicated.

6. REFERENCES

(1) Datos Globales de Donación y Trasplante. (2019). Retrieved from http://www.ont.es/infesp/Paginas/DatosdeDonacionyTrasplante.aspx

(2) Ruiz-Hernández, M., Gómez-Dos Santos, V., Díaz-Pérez, D., Fernández-Alcalde, Hevia-Palacios, V., Álvarez-Rodríguez, S., Burgos-Revilla, F. J. (2019). Experience With Hypothermic Machine Perfusion in Expanded Criteria Donors: Functional Outcomes. Transplantation Proceedings, 51(2), 303–306.

(3) Jiao, B., Liu, S., Liu, H., Cheng, D., Cheng, Y., & Liu, Y. (2013). Hypothermic machine perfusion reduces delayed graft function and improves one-year graft survival of kidneys from expanded criteria donors: A meta-analysis. 8 (12).

(4) Savoye, E., Macher, M-A., Videcocq, M., Gatault. P., Hazzan M. (2017). Evaluation of outcomes in renal transplantation using machine perfusion for the preservation of kidneys from expanded criteria donors. Transplant International, 30 (Supplement 2), 119.

(5) Shen, Y., Cai, R., Sun, J., Dong, X., Huang, R., Tian, S., & Wang, S. (2017). Diabetes mellitus as a risk factor for incident chronic kidney disease and end-stage renal disease in women compared with men: a systematic review and meta-analysis. Endocrine, 55 (1), 66–76.

(6) Modi, Z. J., Lu, Y., Ji, N., Kapke, A., Selewski, D. T., Dietrich, X., Gipson, D. S. (2019). Risk of Cardiovascular Disease and Mortality in Young Adults With End-stage Renal Disease. *JAMA Cardiology*.

(7) Ferenbach, D. A., & Bonventre, J. V. (2016). Acute kidney injury and chronic kidney disease: From the laboratory to the clinic. *Néphrologie & Thérapeutique*, *12*, S41–S48.

(8) Crews, D. C., Bello, A. K., & Saadi, G. (2019). Burden, access, and disparities in kidney disease. *Journal of Nephrology*, *52*, 1–8.

(9) Burlacu, A., Genovesi, S., Ortiz, A., Combe, C., Basile, C., Schneditz, D., … Covic, A. (2019). Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. *Zoological Journal of the Linnean Society*, 1–11.

(10) Cash, E., Graver, A., Kuo, S., Kirkland, G., Hughes, P., Robertson, A., & Jose, M. D. (2019). Why do not all living kidney donor candidates proceed to donation? *Internal Medicine Journal*, *49*(3), 384–387.

(11) Moeckli, B., Sun, P., Lazeyras, F., Morel, P., Moll, S., Pascual, M., & Bühler, L. H. (2019). Evaluation of donor kidneys prior to transplantation: An update of current and emerging methods. *Transplant International*, tri.13430.

(12) Organ Recovery Systems. (n.d.). LifePort Kidney Transporter Operator ' s Manual 1.1

(13) Moers, C., Smits, J. M., Maathuis, M.-H. J., Pirenne, J., Kirste, G. R., Treckmann, J., Rahmel, A. (2008). Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation. *New England Journal of Medicine*.

(14) Moers C, Leuvenink HG, Ploeg RJ. Non-heart beating organ donation: over-view and future perspectives. Transpl Int 2007;20:567-75.

(15) Snoeijs MG, Schaefer S, Christiaans MH, et al. Kidney transplantation using elderly non-heart-beating donors: a single-center experience. Am J Transplant 2006;6:1066-71.

(16) Patel, K., Nath, J., Hodson, J., Inston, N., & Ready, A. (2018). Outcomes of donation after circulatory death kidneys undergoing hypothermic machine perfusion

following static cold storage: A UK population-based cohort study. *American Journal of Transplantation*.

(17) Jochmans I, Moers C, Smits JM, et al. Machine perfusion versus cold stor- age for the preservation of kidneys donated after cardiac death: a multi- center, randomized, controlled trial. *Ann Surg*. 2010;252(5):756-764.

(18) Bathini V, McGregor T, McAlister VC, Luke PP, Sener A. Renal perfu- sion pump versus cold storage for donation after cardiac death kid- neys: a systematic review. *J Urol*. 2013;189:2214.

(19) Deng R, Gu G, Wang D, et al. Machine perfusion versus cold storage of kidneys derived from donation after cardiac death: a meta-analysis. *PLoS ONE*. 2013;8:e56368.

(20) Gallinat, A., Amrillaeva, V., Samuel, U., Paul, A., Benko, T., van Meel, M., … Minor, T. (2016). Reconditioning by end-ischemic hypothermic in-house machine perfusion: A promising strategy to improve outcome in expanded criteria donors kidney transplantation. *Clinical Transplantation*.

(21) Treckmann, J., Moers, C., Smits, J. M., Gallinat, A., Maathuis, M. H. J., Van Kasterop-Kutz, M., … Paul, A. (2011). Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. *Transplant International*.

(22) Matsuoka, L., Mendez, R. G., Selby, R., Shah, T., Mendez, R., Bunnapradist, S., Cho, Y. (2006). Pulsatile Perfusion Reduces the Incidence of Delayed Graft Function in Expanded Criteria Donor Kidney Transplantation. *American Journal of Transplantation*, *6*(6), 1473–1478.

(23) Jochmans, I., Moers, C., Smits, J. M., Leuvenink, H. G. D., Treckmann, J., Paul, A., Pirenne, J. (2011). The prognostic value of renal resistance during hypothermic machine perfusion of deceased donor kidneys. *American Journal of Transplantation*.

(24) Sandal, S., Paraskevas, S., Cantarovich, M., Baran, D., Chaudhury, P., Tchervenkov, J. I., & Sapir-Pichhadze, R. (2018). Renal resistance thresholds during hypothermic machine perfusion and transplantation outcomes – a retrospective cohort study. *Transplant International*.

(25) Le Dinh, H., Weekers, L., Bonvoisin, C., Krzesinski, J. M., Monard, J., De Roover, A., Detry, O. (2012). Delayed Graft function does not harm the future of donation-after-cardiac death in kidney transplantation. *Transplantation Proceedings*, *44*(9), 2795–2802.

(26) Taylor, M. J., & Baicu, S. C. (2010). Current state of hypothermic machine perfusion preservation of organs: The clinical perspective. *Cryobiology*, *60*(3 SUPPL.), S20–S35. Sedigh, A., Tufveson, G., Bäckman, L., Biglarnia, A. R., & Lorant, T. (2013). Initial experience with hypothermic machine perfusion of kidneys from deceased donors in the Uppsala region in Sweden. *Transplantation Proceedings*, *45*(3), 1168–1171.

(27) Moers, C., Ploeg, R., Kox, J., Strelniece, A., Leuvenink, H., Van Heurn, E., Pirenne, J. (2018). The Benefits of Hypothermic Machine Preservation and Short Cold Ischemia Times in Deceased Donor Kidneys. *Transplantation*. Charalampidis, S., Crane, J., Bonatsos, V., Papalois, V., Herbert, P. E., Dor, F. J. M. F., … Muthusamy, A. (2019). Cold Pulsatile Machine Perfusion versus Static Cold Storage in Kidney Transplantation: A Single Centre Experience. *BioMed Research International*, *2019*, 1–8.

(28) Hosgood, S. A., Yang, B., Bagul, A., Mohamed, I. H., & Nicholson, M. L. (2010). A comparison of hypothermic machine perfusion versus static cold storage in an experimental model of renal ischemia reperfusion injury. *Transplantation*, *89*(7), 830–837.

(29) Burgos Revilla, F. J., Hevia, V., Diez, V., Alvarez, S., Gomez, V., Orosa, A., Gomis, A. (2015). Machine Perfusion: Initial Results in an Expanded Criteria Donor Kidney Transplant Program. *Transplantation Proceedings*, *47*(1), 19–22.

(30) Yushkov, Y. Y., Sheth, M., Ying, A., Icitovic, N., Goldstein, M. J., Dikman, S. H., & Stern, J. (2012). Identifying Risk Factors in Renal Allografts before Transplant: Machine-Measured Renal Resistance and Posttransplant Allograft Survival. *Progress in Transplantation*, *22*(2), 175–182.

(31) Gelpi, R., Sole, M., Oppenheimer, F., Adalia, R., Diekmann, F., Ruiz, A., Rodríguez-Villar, C. (2018). The development of a predictive model of graft function in uncontrolled donors after circulatory death: validity of a pulsatile renal preservation machine cut-off value for kidney acceptance. *Nephrology Dialysis Transplantation*, 1–7.

(32) Hameed, A. M., Pleass, H. C., Wong, G., & Hawthorne, W. J. (2016). Maximizing kidneys for transplantation using machine perfusion. *Medicine*, *95*(40), e5083.

(33) Paloyo, S., Sageshima, J., Gaynor, J. J., Chen, L., Ciancio, G., & Burke, G. W. (2016). Negative impact of prolonged cold storage time before machine perfusion preservation in donation after circulatory death kidney transplantation. *Transplant International*, *29*(10), 1117–1125.

(34) Peng, P., Ding, Z., He, Y., Zhang, J., Wang, X., & Yang, Z. (2018). Hypothermic Machine Perfusion Versus Static Cold Storage in Deceased Donor Kidney Transplantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Artificial Organs*, *0*(0), 1–12.

(35) Figueiredo Rodrigo, M., Moir John, A., Talbot, D., & Wilson Colin, H. (2015). Normothermic and hypothermic machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. *Cochrane Database of Systematic Reviews*, (5).

(36) Gok, M. A., Pelzers, M., Glatz, J. F. C., Shenton, B. K., Buckley, P. E., Peaston, R., Talbot, D. (2003). Do tissue damage biomarkers used to assess machine-perfused NHBD kidneys predict long-term renal function post-transplant? *Clinica Chimica Acta*, *338*(1–2), 33–43.

(37) Dion, M. S., Luke, P. P., McGregor, T. B., Sener, A., & McAlister, V. C. (2014). Hypothermic machine perfusion improves Doppler ultrasonography resistive indices and long-term allograft function after renal transplantation: a single-centre analysis. *BJU International*, *116*(6), 932–937.

(38) Ludwig, C., Ready, A. R., Inston, N. G., Nath, J., Guy, A. J., Tennant, D. A., & Cobbold, M. (2014). Metabolomic Analysis of Perfusate During Hypothermic Machine Perfusion of Human Cadaveric Kidneys. *Transplantation*, *99*(4), 754–759.

(39) Parikh, C. R., Hall, I. E., Bhangoo, R. S., Ficek, J., Abt, P. L., Thiessen-Philbrook, H., Reese, P. P. (2016). Associations of Perfusate Biomarkers and Pump Parameters with Delayed Graft Function and Deceased Donor Kidney Allograft Function. *American Journal of Transplantation*, *16*(5), 1526–1539.

(40) Xue, W.-J., Xiang, H.-L., Li, Y., Tian, X.-H., Ding, C.-G., Tian, P.-X., Zheng, J. (2018). Predictive Score Model for Delayed Graft Function Based on Hypothermic Machine Perfusion Variables in Kidney Transplantation. *Chinese Medical Journal*, *131*(22), 2651–2657.

(41) Liu, H., Yin, H., Wang, W., Hu, X., Xie, D., & Zhang, X. (2017). Effect of Hypothermic Machine Perfusion on the Preservation of Kidneys Donated After Cardiac Death: A Single-Center, Randomized, Controlled Trial. *Artificial Organs*, *41*(8), 753–758.

(42) Gómez, V., Galeano, C., Diez, V., Bueno, C., Díaz, F., & Burgos, F. J. (2012). Economic impact of the introduction of machine perfusion preservation in a kidney transplantation program in the expanded donor era: Cost-effectiveness assessment. *Transplantation Proceedings*, *44*(9), 2521–2524.

(43) San Miguel, L., Roberfroid, D., Stordeur, S., & Swartenbroekx, N. *Machine perfusion in kidneys from deceased donors – A rapid assessment*.

(44) Wight, J., Chilcott, J., Holmes, M., & Brewer, N. (2003). Pulsatile machine perfusion versus cold storage of kidneys for transplantation, *7*(25).

(45) Pirenne, J., Groen, H., Moers, C., Monbaliu, D., Smits, J. M., Paul, A., … Ploeg, R. J. (2012). Cost-Effectiveness of Hypothermic Machine Preservation Versus Static Cold Storage in Renal Transplantation. *American Journal of Transplantation*, *12*(7), 1824–1830.

(46) Wight J, Chilcott J, Holmes M, et al. The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. Health Technol Assess. 2003;7:1–94.