



Review

Advances in Kidney Transplant, Machine Perfusion, and Viability Markers

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Abstract

Despite improvements in kidney transplantation rates, the shortage of donor kidneys remains a critical issue, exacerbated by non-utilization of recovered kidneys due to quality concerns, necessitating advancements in perfusion methods to enhance graft outcomes and usage. Although static cold storage remains the default standard for kidney preservation, newer methods like hypothermic machine perfusion have shown improved outcomes, including reduced delayed graft function and better survival rates. Hypothermic oxygenated machine perfusion and normothermic machine perfusion offer some potential clinical benefits but studies to date have demonstrated mixed results. In the United States, LifePort and the XVIVO's Kidney Assist Transport are the most popular hypothermic perfusion devices, with NMP devices mostly in trials. Combining perfusion with biomarkers such as mitochondrial flavin mononucleotide, neutrophil gelatinase-associated lipocalin, and osteopontin shows promise in assessing kidney viability and predicting post-transplant outcomes, though further research is also needed. Emphasis on repair biomarkers, such as uromodulin and osteopontin, aims to better predict graft outcomes and develop new therapies. While notable advancements have been made in the use of machine perfusion and viability testing for liver transplantation, additional research with larger sample sizes is essential to substantiate these results and enhance kidney transplantation outcomes.

Keywords: kidney transplant; machine perfusion; kidney biomarkers; viability assessment; deceased donor



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1. Introduction

While kidney transplantation significantly improves patient survival and overall quality of life, the scarcity of available kidney allografts remains a critical challenge. There are approximately 150,000 patients in the United States currently waitlisted for kidney transplant [1]. Since 2015, the number of kidney allografts has risen steadily through a rise in deceased donation (from 12,250 to 21,340 in 2024), while the number of living donor kidneys has remained unchanged at about 6400 per year since approximately 2003. This number of available donor kidneys falls far short of the need and of the individuals waiting for a kidney transplant, fewer than 30,000 receive one each year [1]. Adding to the already

high number of people waiting for a kidney transplant, over 25% of kidneys recovered are not transplanted, often due to concerns related to organ quality and post-transplant viability. Non-utilization rates are notably higher for kidneys coming from older donors, donors with a history of diabetes and hypertension, donor terminal creatinine greater than 1.5 ng/mL, donation after circulatory death (DCD) donors, and those kidneys undergoing a biopsy at the time of recovery [1–4]. We will review how advancements in perfusion methods have led to the improvement of graft outcomes and subsequently have helped increase the utilization rate of kidney grafts.

2. Kidney Perfusion

For over 50 years, static cold storage (SCS) has been the standard technique for organ preservation [5,6]. SCS reduces metabolic activity causing reduced enzymatic activity and a subsequent reduction in adenosine triphosphate (ATP) consumption. Over time however, energy depletion and increased intracellular acidosis leads to cell swelling and cell death [5,7]. Preservation solutions, such as histidine-tryptophan-ketoglutarate (HTK) and University of Wisconsin (UW), are used to slow down the process of ischemia. Due to the growing demand for kidney transplants and the ongoing organ shortage, there is a need to broaden the use of kidneys from DCD donors as well as from donors meeting expanded criteria (ECD). These kidneys are more susceptible to ischemia–reperfusion injury (IRI) which in turn is a risk factor for primary non-function (PNF), delayed graft function (DGF), graft failure, and non-utilization [8,9]. While hypothermic machine perfusion (HMP) for kidney allografts has been available for over 50 years, rising donor age, presence of donors with more medical complexity, complex logistics leading to higher cold ischemia time (CIT), and the need to reduce IRI, have all led to a renewed interest in preservation modalities including hypothermic oxygenated machine perfusion (HOPE) and normothermic machine perfusion (NMP) (Table 1) [5,6].

Table 1. Characteristics, benefits, and limitations of different perfusion techniques.

	Preservation Temperature (°C)	Oxygenation	Preservation Time (Hours)	Key Benefits	Limitations
SCS	0–4	No	Up to 24 (ideally)	Low cost Simple to operate Easy to transport	Higher risk of IRI
HMP	1–10	No	24–36	Reduces IRI Reduces rates of DGF	High cost Logistics Technical difficulties Need for trained personnel
HOPE	1–10	Yes	Variable	Reduces IRI ATP restoration	Mixed outcomes High cost Logistics Technical difficulties Need for trained personnel
NMP	12–37	Yes	1–4	Reduces IRI Physiologic function Viability assessment Upregulation of repair pathways	Ongoing clinical trial Upregulation of inflammatory pathways Very high cost Logistics Technical difficulties Need for trained personnel

Abbreviations: ATP, adenosine triphosphate; DGF, delayed graft function; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; IRI, ischemic reperfusion injury; NMP, normothermic machine perfusion; SCS, static cold storage.

2.1. Hypothermic Machine Perfusion

Using technology developed in the 1960s, HMP uses a continuous pulsatile low-pressure flow of cold (usually between 2 °C and 8 °C) preservation solution that washes out residual blood and metabolites from the kidney graft [10]. Similarly to the solutions used in SCS, the preservation solution consists of substrates that protect the graft and delivers basic components for renal metabolism under cold ischemia. Pulsatile flow from the HMP, which is similar to physiological perfusion, reduces the depolarization of the endothelial cellular membrane, decreases the formation of toxic free radicals, and increases microvascular vasodilation, thus reducing perfusion resistance, and improving graft viability. HMP also results in a decrease in the production of damage-associated molecular pattern (DAMPs) molecules, which reduces the pro-inflammatory cascade and can reduce the overall severity of ischemia–reperfusion injury [6,11]. Studies have compared the outcomes of kidney transplants between HMP and SCS and have shown that, compared to SCS, grafts perfused with HMP have decreased risk of DGF and improved graft survival. In their international randomized controlled trial, Moers et al. showed that the use of HMP decreased the rate of DGF compared to SCS (adjusted odds ratio 0.57, $p = 0.01$) and one-year graft survival was superior in the HMP group in comparison to SCS (94% vs. 90%, $p = 0.04$) [12]. In another international randomized study, Treckmann et al. [13] looked at ECD kidney from brain dead donors. HMP preservation had a lower risk of DGF compared to the SCS group (odds ratio 0.46, $p = 0.047$), the incidence of non-function was lower in the HMP group than in the SCS group (3% vs. 12%, $p = 0.04$) and one-year graft survival was higher in the HMP group than in the SCS group (92.3% vs. 80.2%, $p = 0.02$). Similarly, Jochmans et al. [14] compared the outcomes of DCD kidneys and found that the rate of DGF was lower in the HMP group than in the SCS group (adjusted odds ratio 0.43, $p = 0.025$). However, one-year graft and patient survival rates were similar in both HMP and SCS groups (93.9% vs. 95.1%, $p = 0.7$).

The use of HMP has also allowed longer preservation times for kidney allografts in situations requiring more complex logistics (longer recipient travel time, multi-organ transplants) while maintaining good graft outcomes, even in grafts with higher risk (DCD, ECD). In their analysis, Gill et al. [15] examined how perfusion affected DGF rates within each kidney group, including standard criteria donors (SCD), ECD, and DCD, and within groups of CIT divided into increments of 6 h. Their results showed that the use of perfusion, compared to SCS, decreased the risk of DGF across all CIT groups for SCD grafts. In the ECD group, perfusion showed a decreased risk of DGF compared to SCS in the CIT group after 6 h. In the DCD group, the use of perfusion only showed a decreased risk of DGF compared to SCS in the CIT group between 6 and 24 h.

2.2. Hypothermic Oxygenated Machine Perfusion

HOPE, which is a different type of cold perfusion, has also been investigated. It involves the addition of oxygenation to the standard HMP, which can be infused directly into the perfusion solution or added by an external membrane oxygenator [10]. The addition of oxygen is thought to restore mitochondrial function by restoring ATP generation, thereby reducing oxidative stress and decreasing IRI [16]. This is thought to be of particular value for DCD kidneys, which would have undergone a period of hypotension, poor perfusion in the donor, and warm ischemia [17].

In assessing the value of added oxygenation for perfusion, in their multicenter European randomized, double-blind, controlled (COMPARE) trial, Jochmans et al. found that in DCD kidneys with donor age over 50 years, HOPE grafts in comparison to HMP grafts, had fewer severe post-operative complications (11% vs. 16%, $p = 0.032$), less biopsy-proven acute rejection (14% vs. 26%, $p = 0.04$), and lower rates of one-year graft loss (3% vs. 10%, $p = 0.028$), although there were no differences in one-year estimated glomerular filtration

rate, or one-year patient survival rate [10,17]. Despite these results showing great promise, other studies have not been able to replicate those results. For instance, Pravisani et al., in their retrospective study, examined kidneys perfused on HMP (n = 52) compared to HOPE (n = 51) and found no differences in DGF (25% vs. 21.5%, $p = 0.58$), vascular complications (0.2% vs. 0.2%, $p > 0.99$), urological complications (11.5% vs. 13.7%, $p = 0.77$), or episodes of graft rejection (7.7% vs. 11.7%, $p = 0.52$) between HMP and HOPE, respectively. At one-year post-transplant, serum creatinine levels were comparable between HMP and HOPE [18].

Moreover, the benefits of HOPE over SCS have not yet been clearly established. In their randomized, multicenter study, Husen et al. [19] compared outcomes from ECD kidneys on SCS alone compared to SCS and HOPE and found no differences in one-year graft survival in the HOPE group compared to the SCS group (92.1% vs. 93.3%, $p = 0.71$). There were also no differences in the rates of DGF, PNF, estimated glomerular filtration rate (eGFR), or acute rejection between the groups. Although studies have shown that adding oxygen to HMP is both safe and feasible, there are still many investigational questions such as the optimal amount of oxygen, the duration of perfusion, and the method of oxygen delivery during HOPE [5,16]. Additional studies are needed to understand all the potential benefits of HOPE over HMP [10].

2.3. Normothermic Machine Perfusion

The recent introduction and utilization of NMP represents an innovative approach aimed at maintaining the graft in an environment closely resembling its physiological condition. This method supplies essential metabolic substrates at normothermic temperatures [6,10]. NMP is thought to promote cellular metabolism, repair pathways, restock ATP and promote graft preservation [10,16]. Solutions used for NMP include oxygenated red blood cells solution or solutions containing supplements that protects the graft against the inflammatory injury caused by reperfusion ischemia [16].

In recent years, NMP technologies have gained enthusiasm as effective tools for organ preservation and transplantation, particularly for liver transplantation [20,21]. Early data suggested that kidneys preserved with a short period of NMP showed improved metabolic function and reduced tubular damage compared to those stored in cold storage. Although inflammatory cytokine levels were similar between groups, IL-6 and heat shock protein 70 were increased after NMP [22]. These findings suggest that NMP may reduce ischemia–reperfusion injury in kidney allografts by upregulated protective mechanisms.

Despite this knowledge and promising studies showing improvement of outcomes for liver transplants using NMP, the outcomes for kidney transplants have been mixed [6]. For instance, Nicholson et al. compared the outcomes of extended criteria kidneys perfused on NMP with grafts preserved by SCS and found that NMP grafts had lower rates of DGF compared to SCS grafts (5.6% vs. 36.2%, $p = 0.014$); however, there were no differences in one-year graft or patient survival [23]. By comparison, in a larger randomized controlled trial, Hosgood et al. [24] compared 168 kidneys from DCD preserved using SCS to 170 kidneys from DCD preserved first with SCS and then with one hour of NMP. They found no significant difference in DGF rates between the two methods (58.5% vs. 60.7%, $p = 0.624$). Additionally, a study assessing the benefit of NMP compared to HMP by Mazilescu et al. [25] compared kidneys initially perfused with HMP and placed on 1 to 3 h of NMP (n = 13) with kidneys perfused with HMP alone (n = 26). There were no differences in DGF rates between the HMP with NMP and HMP alone groups (30.8% vs. 46.2%, $p = 0.51$). There were also no differences in one-year graft or patient survival between the two groups.

The maintenance of a physiological environment can be challenging, especially when prolonged duration of perfusion might be needed. Disruptions to homeostasis can come from potential rapid volume changes (urine production) leading to electrolytes and pH

imbalance, intolerance to hemolysis from the circuit, and the concern that disruption of oxygen metabolism in the graft can lead to future renal dysfunction [26,27]. In their study, Weissenbacher et al. [27] used discarded human kidneys and perfused them for up to 24 h on NMP. They compared the effects on perfusate electrolytes content between kidneys whose volume loss (from urine production) was replaced with lactated Ringer's solution and kidneys who were perfused using urine recirculation. They found that the kidneys that did not use urine recirculation had greater pH imbalance, and the kidneys stopped producing urine at around 4–6 h after NMP was initiated. On the other hand, the kidneys that used urine recirculation had more stable pH, physiologic sodium levels in the perfusate and had urine production for the full 24 h they were on NMP. While these kidneys were not transplanted, it did show the feasibility of perfusing kidneys with NMP for longer periods of time. In another study, Dumbill et al. [26] demonstrated that they were able to perfuse 36 kidneys for up to 24 h on NMP prior to safely transplanting them. However, they did not see significant differences between post-transplant outcomes between the NMP kidneys and their control group. Nonetheless, the ability to perfuse for longer period of time showed that there is potential to investigate the function of the graft and assess levels of biomarkers that could help predict future graft function. Future applications for NMP may also include the administration of drug therapies aimed at organ reconditioning [16].

At present, there are no standardized protocols for NMP in kidney transplantation. Approaches differ widely in both how long perfusion lasts and what solutions are used [26,28–30]. Thus far, various approaches have been employed, each with distinct mechanisms, logistical considerations, and future requirements in both experimental and clinical contexts. In the United States, NMP for kidneys has been used to evaluate and improve organ quality before transplant. However, to date, access to NMP kidney devices remains limited. Unlike its established use in liver, heart, and lung transplants, NMP for kidneys remains largely experimental due to technical challenges. To date, only a few kidney NMP devices have been fully developed. The Kidney Assist device is certified for use in Europe [30]. It works by controlling pressure and can maintain temperatures between 12 and 37 °C, allowing for different types of kidney perfusion. Kidneys can be preserved cold for 24 h or at body temperature for up to 6 h. OrganOx Metra K, developed by OrganOx Ltd. (Oxford, UK), is a portable kidney NMP device designed for prolonged periods of perfusion. Safety and feasibility have been shown in a phase I, non-randomized, single-center study [26]. Other NMP kidney devices are also currently being developed and are under trial [31]. As research and development advance, NMP holds significant promise to transform kidney transplantation by improving graft outcomes and expanding preservation options.

In summary, HMP uses cold preservation solutions to improve kidney graft outcomes by reducing toxic radicals and inflammation. Studies have shown that HMP decreases the risk of DGF and improves graft survival compared with SCS. HOPE, which adds oxygen to HMP, has shown promising results in reducing post-operative complications and graft loss; but has mixed outcomes in other studies. NMP mimics physiological conditions and supports metabolic functions with varying success in kidney transplants; however, it holds potential for viability assessment and drug therapies (Table 2).

Table 2. Overview of clinical studies comparing different types of perfusion techniques.

	Type of Study	Comparison	Study Groups	Type of Donors	Key Outcomes	Results
Moers et al. 2009 [12]	Randomized controlled trial	SCS vs. HMP	SCS, n = 336 HMP, n = 336	Deceased donor	DGF PNF Graft and patient survival	HMP decreased rate of DGF (adjusted odds ratio 0.57, $p = 0.01$) HMP improved 1-year allograft survival (94% vs. 90%, $p = 0.04$)
Treckmann et al. 2011 [13]	Randomized controlled trial	SCS vs. HMP	SCS, n = 91 HMP, n = 91	ECD	DGF Non-function Graft survival	HMP decreased rate of DGF (odds ratio 0.46, $p = 0.047$) HMP decreased rate of non-function (3% vs. 12%, $p = 0.04$) HMP improved 1-year graft survival (92.3% vs. 80.2%, $p = 0.02$)
Jochmans et al. 2010 [14]	Randomized controlled trial	SCS vs. HMP	SCS, n = 82 HMP, n = 82	Deceased donor	DGF	HMP decreased rate of DGF (adjusted odds ratio 0.43, $p = 0.025$)
Gil et al. 2014 [15]	Retrospective analysis	SCS vs. HMP	Standard criteria donors, n = 7192 ECD, n = 15,122 DCD, n = 8395 CIT groups: Increments of 6 h from 0 to 36 h	Standard criteria donors ECD DCD	DGF within each donor group by CIT categories	Standard criteria donor group: adjusted odds of DGF lower with HMP across all CIT groups ECD group: adjusted odds of DGF lower with HMP with CIT > 6 h DCD group: adjusted odds of DGF lower with HMP with CIT between 6 and 24 h
Jochmans et al. 2020 [17]	Randomized controlled trial	HMP vs. HOPE	HMP, n = 106 HOPE, n = 106	DCD	One-year eGFR Post-operative complications Acute rejection Graft and patient survival	There were no differences in 1-year eGFR or 1-year patient survival in the HOPE group compared to the HMP group HOPE decreased rate of severe post-operative complications (11% vs. 16%, $p = 0.032$) HOPE decreased rate of acute rejection (14% vs. 26%, $p = 0.04$) HOPE decreased rate of 1-year graft loss (3% vs. 10%, $p = 0.028$)
Pravisani et al. 2022 [18]	Retrospective analysis	HMP vs. HOPE	HMP, n = 52 HOPE, n = 51	DBD ECD	DGF Vascular and urologic complications Graft rejection One year creatinine serum levels	There were no differences in rates of DGF, vascular complications, urologic complications, episodes of graft rejection or 1-year serum creatinine levels between the HOPE group and the HMP group
Husen et al. 2021 [19]	Randomized controlled trial	SCS vs. HOPE	SCS, n = 135 HOPE, n = 127	ECD	DGF PNF Acute rejection Graft survival	There were no differences in rates of DGF, PNF, acute rejection or graft survival between the HOPE group and the HMP group

Table 2. Cont.

	Type of Study	Comparison	Study Groups	Type of Donors	Key Outcomes	Results
Nicholson et al. 2013 [23]	Prospective study	SCS vs. NMP	SCS, n = 47 NMP, n = 18	ECD	DGF Graft and patient survival	There was no difference in graft or patient survival between the NMP and SCS groups NMP decreased rate of DGF (5.6% vs. 36.2%, $p = 0.014$)
Hosgood et al. 2023 [24]	Randomized controlled trial	SCS vs. NMP	SCS, n = 168 NMP, n = 170	DCD	DGF	There was no difference in rate of DGF between the NMP and SCS groups (58.5% vs. 60.7%, $p = 0.624$)
Mazilescu et al. 2022 [25]	Prospective study	HMP vs. HMP + NMP	HMP, n = 26 HMP + NMP, n = 13	DBD DCD	DGF Graft and patient survival	There were no differences in rate of DGF or one-year graft and patient survival between the HMP and HMP + NMP groups

Abbreviations: CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; NMP, normothermic machine perfusion; PNF, primary non-function; SCS, static cold storage.

Further research is necessary to identify the optimal preservation methods for various types of kidney transplants. This includes evaluating the cost-effectiveness and logistical practicality of different preservation techniques [5,16]. Additionally, research also shows that perfusion characteristics have to be interpreted within clinical context. In their study, Guarrera et al. showed that kidneys transplanted after poor perfusion numbers (flow < 80 mL/min and resistance > 0.4 mmHg/mL/min) can still achieve acceptable short and long-term outcomes [32]. There are no standardized perfusion protocols hence interpretation of perfusion parameters should not be performed in isolation and additional information such as donor history and comorbidities, warm ischemic time, and biopsy findings should also be taken into account [33,34].

Finally, a few studies (mostly animal studies) have investigated additional perfusion modalities such as controlled oxygenated rewarming and subnormothermic machine perfusion. The initial promising results have encouraged additional studies on human organs; however, larger controlled trials are needed in the future to assess the applicability of these perfusion technologies [6].

2.4. Current Perfusion Devices

In the United States, LifePort and the Kidney Assist Transport device developed XVIVO are among the most used devices for hypothermic perfusion. Early studies have shown that the perfusion temperatures for kidneys were kept between 2 °C and 8 °C [10]. More recently, studies on different organs have demonstrated that keeping the temperature closer to 10 °C might be more beneficial [35,36]. Current hypothermic devices perfuse the kidneys between temperatures of 1 °C and 10 °C.

Several NMP devices are available for kidneys, although most are still in the clinical trial phase. Current perfusion devices are presented in Table 3.

Table 3. Kidney perfusion devices.

	LifePort	Kidney Assist Transport (XVIVO)	RM4 (IGL)	Paragonix Kidney Vault	Kidney Assist (XVIVO)	ARK Kidney (Ebers—Undergoing Clinical Trial)
Flow	Pulsatile	Pulsatile	Pulsatile	Pulsatile	Pulsatile	Pulsatile
Number of grafts	1 kidney	1 kidney	1–2 kidneys	1 kidney	1 kidney	1 kidney
Hypothermic or Normothermic	Hypothermic	Hypothermic	Hypothermic	Hypothermic	Normothermic	Normothermic
Oxygen	Optional	Yes	Yes	No	Yes	Yes
Temperature range (° C)	1–8	2–10	2–8	4–8	12–37	15–30
Key variables measured	Pressure, Flow rate, Resistance, Temperature	Pressure, Flow rate, Resistance, Temperature	Pressure, Flow rate, Resistance, Temperature	Pressure, Flow rate, Resistance, Temperature, Location tracking	Pressure, Flow rate, Resistance, Temperature	Not reported
Adjustable variables	Pressure	Pressure	Pressure	None	Pressure, Temperature, Oxygen	Not reported
Weight (kg) (fully loaded)	20.4	28.4	20.0	11.3	68.0	Not reported
Dimension (cm)	61.96 × 36.83 × 36.2	61.5 × 39.5 × 34	51 × 37.8 × 21.9	45.72 × 40.64 × 43.18	112 × 92.5 × 62.5	54.0 × 90.0 × 52.5
Regulatory status	FDA cleared	FDA cleared	FDA cleared	FDA cleared	CE marked *	CE marked *

Abbreviations: FDA, Food and Drug Administration. * CE marked: affirms its compliance with the relevant European Union legislation and the product may be sold anywhere in the European Economic Area.

3. Viability Markers

Whereas many advancements have been made in transplantation, methods for evaluating kidney allograft viability remain limited. Most transplant centers rely on donor history, laboratory results, organ appearance after recovery, biopsy data, and simple perfusion parameters when available. Owing to the increasing gap between the number of available donor kidneys and the number of patients on the waiting list, transplant centers have been using kidney grafts that are more vulnerable to prolonged DGF, suboptimal allograft function, and PNF. As a result, there remains a huge clinical need to assess kidney allograft viability more accurately [2–4].

3.1. Perfusion Technology and Biomarkers

Combining perfusion technology with biomarkers has proven effective in predicting liver viability and increasing utilization rates. This innovative approach is now being applied to kidney transplants and shows great potential for improving outcomes in this area. Perfusion technology and biomarkers such as mitochondrial flavin mononucleotide (FMN), neutrophil gelatinase–associated lipocalin (NGAL), uromodulin (UMOD), osteopontin (OPN), ATP synthase subunit b (ATPSb), and cell-free mitochondrial DNA (cf-mtDNA) can help assess kidney allograft viability and predict post-transplant outcomes (Table 4). Studies assessing FMN in kidney transplantation remain limited, although the use of perfusion in kidney transplantation has been shown to improve both DGF and outcomes [12,17,37]. Van de Leemkolk et al. [38] assessed 109 kidney allografts on HOPE originating from DCD donors older than 50 years. The median CIT was relatively short (10–11 h), and perfusion times were approximately 7 h. Within this European cohort, no correlation was observed between post-transplant outcomes and FMN perfusate levels, although both the donor and transplant characteristics were conservative and FMN perfusate levels specific to PNF cases were not reported [17,38]. In a second European study, FMN concentrates in perfusates collected during NMP were collected. Seven out of eleven kidneys were transplanted, and in that small cohort, FMN levels at 6 min of NMP were significantly higher in the allografts that developed DGF and PNF [39]. Despite the more favorable donor and transplant characteristics in both studies, PNF rates were notably higher than those reported in the United States (4% and 28%) and study cohorts were small suggesting population differences and the need for additional investigation [38,39].

Table 4. Emerging viability biomarkers in kidney perfusion.

	Source	Function	Correlation with Outcomes	Strengths	Limitations
FMN	Perfusate	Mitochondrial injury	Increased levels linked to increased rates of DGF and PNF	Non-invasive	Limited data
NGAL	Urine	Tubular injury	Increased levels linked to increased rate of DGF	Widely studied	Poor specificity
ATPSb	Perfusate	Mitochondrial health	Decreases IRI	Novel target	Limited clinical validation
UMOD	Urine	Tubular repair	Decreased levels linked to increased risk of AKI Increased levels linked to increased risk of graft failure	Potential repair marker	Not perfusate tested
OPN	Urine	Inflammation repair	Increased levels linked to increased risk of AKI Increased levels linked to lower risk of graft failure	Complementary to UMOD	Not perfusate tested

Abbreviations: AKI, acute kidney injury; ATPSb, ATP synthase subunit b; DGF, delayed graft function; FMN, flavin mononucleotide; IRI, ischemic reperfusion injury; NGAL, neutrophil gelatinase–associated lipocalin; OPN, osteopontin; PNF, primary non-function; UMOD, uromodulin.

3.2. Kidney Injury Biomarkers

Kidney allografts with a high terminal creatinine, also referred to as acute kidney injury (AKI), continue to be at a high risk for non-utilization at the time of recovery [1]. To date, many potential AKI kidney biomarkers have been identified (Figure 1) [40,41].

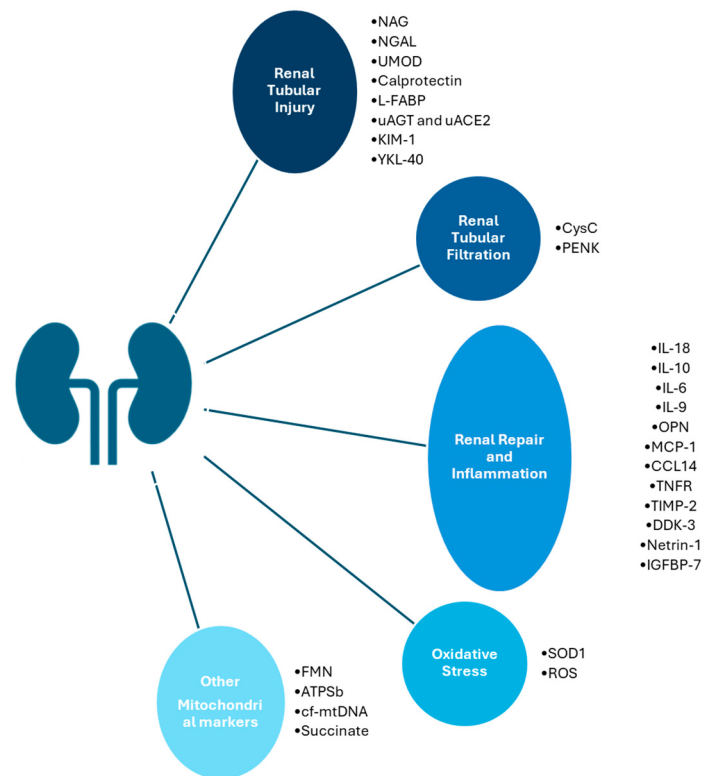


Figure 1. Kidney injury biomarkers. Abbreviations: ATPSb, ATP synthase subunit b; CCL14, chemokine ligand 14; cf-mtDNA, cell-free mitochondrial DNA; CysC, cystatin C; DDK-3, Dickkopf-Related Protein 3; FMN, flavin mononucleotide; IGFBP-7, insulin-like growth factor-binding protein 7; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; MCP-1, monocyte chemoattractant protein-1; NAG, N-acetyl- β -D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; PENK, proenkephalin; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; TNFR, tumor necrosis factor receptor; TIMP-2, tissue inhibitor of metalloproteinases 2; uACE2, urinary angiotensin-converting enzyme 2; uAGT, urinary angiotensinogen; UMOD, uromodulin; YKL-40, chitinase-3-like protein 1.

Mitochondrial dysfunction is a key feature of IRI. IRI and AKI lead to the loss of renal cortical mitochondrial proteins such as ATPSb, resulting in the release of cf-mtDNA. ATPSb and cf-mtDNA serve as potential biomarkers of interest as well as future therapeutic targets for intervention [42]. Studies investigating the ability of injury markers to predict graft failure have shown mixed success. Even though NGAL, kidney injury molecule-1 (KIM-1), IL-18, and liver-type fatty acid binding protein (L-FABP) have been shown to be accurate markers of ischemic kidney injury and predictors of DGF in transplant, they have failed to show a strong correlation with kidney transplant outcomes (Figure 2) [40–44]. In a study investigating injury markers in deceased donor urine, higher levels of NGAL in donor urine were linked to a greater risk of DGF in recipients [43]. While higher levels of NGAL and L-FABP in urine were associated with slightly lower kidney function at 6 months, this proved to be true only in recipients who did not experience DGF [43].

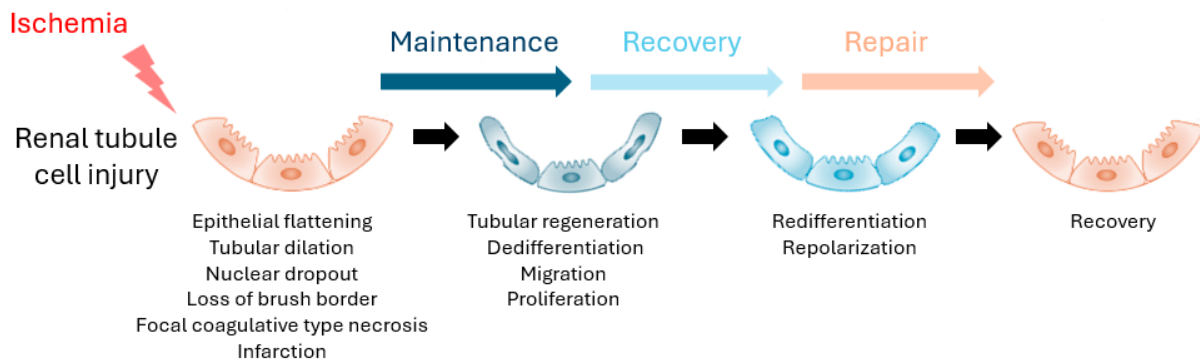


Figure 2. Adaptive kidney repair mechanism. Image adapted from: Andrianova NV, Buyan MI, Zorova LD et al. [44] Kidney Cells Regeneration: Dedifferentiation of Tubular Epithelium, Resident Stem Cells and Possible Niches for Renal Progenitors. *Int. J. Mol. Sci.* **2019**, *20*, 6326. Published 15 December 2019. doi:10.3390/ijms20246326.

3.3. Kidney Repair Biomarkers

More recent studies have shifted focus to repair biomarkers and their role in predicting transplant outcomes with the hypothesis that kidney allografts that come from donors with activated “adaptive proteins” will repair well when transplanted into a recipient with an uneventful post-transplant course (Figure 2).

Therefore, measuring how well a kidney repairs itself may be more useful than simply noting how injured it is. Two promising repair biomarkers include UMOD, a protein expressed in the kidney by cells of the thick ascending limb and early distal convoluted tubules and OPN, a protein present in the loop of Henle and distal tubule. In a study investigating the level of UMOD and OPN in deceased donor urine, donor urine UMOD concentrations were significantly lower with increasing AKI stages, whereas levels of urine OPN increased with worsening AKI [45,46]. The study found that higher UMOD levels in donor urine were linked to a higher risk of graft failure in recipients. Conversely, higher OPN levels in donor urine are associated with a lower risk of graft failure [45]. Additional investigations on UMOD and OPN within the perfusion perfusate are yet to be completed but are underway.

4. Summary

Despite advancements in transplantation, methods to evaluate kidney allograft viability are limited, leading to the use of more vulnerable kidney grafts with risks, such as prolonged DGF and PNF. Combining perfusion technology with biomarkers has shown the potential for improving kidney transplant outcomes, although biomarker studies remain limited. Kidney injury biomarkers such as NGAL and ATP5b serve as indicators of ischemic injury, but their correlation with transplant outcomes is mixed. Recent focus has shifted to repair biomarkers, such as UMOD and OPN, which may better predict how well kidney allografts will repair post-transplant, providing new avenues for improving kidney transplant success. Together, perfusion technology and biomarkers hold promise for assessing kidney transplant viability, predicting post-transplant outcomes, reducing organ non-utilization, and providing targets for future treatment. However, further studies with larger populations are essential to validate these findings.

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Abbreviations

The following abbreviations are used in this manuscript:

AKI	acute kidney injury
ATP	adenosine triphosphate
ATPSb	ATP synthase subunit b
cf-mtDNA	cell-free mitochondrial DNA
CIT	cold ischemia time
DAMPs	damage-associated molecular pattern
DGF	delayed graft function
DCD	donation after circulatory death
ECD	expanded criteria donor
eGFR	estimated glomerular filtration rate
FMN	flavin mononucleotide
HMP	hypothermic machine perfusion
HTK	histidine-tryptophan-ketoglutarate
HOPE	hypothermic oxygenated machine perfusion
IRI	ischemic reperfusion injury
KIM-1	kidney injury molecule-1
L-FABP	liver-type fatty acid binding protein
NGAL	neutrophil gelatinase-associated lipocalin
NMP	normothermic machine perfusion
OPN	osteopontin
PNF	primary non-function
SCD	standard criteria donors
SCS	static cold storage
UMOD	uromodulin
UW	University of Wisconsin

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