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“Time is tissue” – a minireview on the importance of donor nephrectomy, donor hepatectomy and implantation times in kidney and liver transplantation

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Abbreviations

aHR = adjusted hazard ratio

aOR = adjusted odds ratio

CI = confidence interval

DBD = donation after brain death

DCD = donation after circulatory death

DGF = delayed graft function

DRI = donor risk index

EAD = early allograft dysfunction

EGF = early graft function

eGFR = estimated glomerular filtration rate

HA = hepatic artery

IC = ischemic cholangiopathy

IQR = interquartile range

MEAF = model for early allograft function

PNF = primary non-function

POD = postoperative day

PV = portal vein

n.a. = not available

SD = standard deviation

SE = standard error

SGF = slow graft function

Abstract

Donor organs are exposed to sequential temperature changes during the transplantation process. The role of donor warm ischemia and cold ischemia times on post-transplant outcomes has been extensively studied. Much less attention has been paid to the transient ischemia occurring during donor organ removal and implantation. Recently, it has become clear that prolonged donor nephrectomy and implantation time are independently associated with delayed graft function after kidney transplantation. In addition, implantation time correlates with post-transplant kidney graft function, histology, and survival. Similar detrimental associations of donor hepatectomy and implantation time with early allograft dysfunction, ischemic cholangiopathy, and graft and patient survival after liver transplantation have been demonstrated. This review details kidney and liver temperature changes occurring during procurement and transplantation. It summarizes the effects of the ischemia the kidney and liver sustain during these phases on short- and long-term post-transplant outcomes, advocating the standardized reporting of donor hepatectomy, donor nephrectomy, and implantation times in (inter)national registries. The review also explores strategies to protect the graft from this ischemic injury.

Introduction

Transplantation is a race against the clock because of ischemia. Efforts to limit the consequences of ischemia are focused on the preservation phase, ranging from reducing cold ischemia time to different organ perfusion techniques. In donation after circulatory death (DCD), donor warm ischemia (at body temperature) prior to *in situ* cooling has also been extensively studied. By comparison, ischemia at temperatures below normothermia but above deep hypothermia (0°C–4°C) has received little attention. This ischemia occurs during 4 phases of the transplantation process: (a) organ removal (recovery ischemia), (b) donor and (c) recipient back-table (back-table ischemia), and (d) organ implantation (implantation ischemia) (Fig. 1, defining terminology). The ischemia sustained during these phases can be detrimental to post-transplant kidney and liver outcomes despite the short duration (range of tens of minutes) compared to the hours of cold ischemia because the organs remain at relatively high temperatures in a hypoxic environment.

This review details temperature changes of the kidney and liver throughout the transplantation process. It summarizes the effects of ischemia during these 4 phases on short- and long-term post-transplant outcomes and discusses strategies that might protect the graft.

Organ temperatures throughout the transplantation process

In situ organ cooling, started by cold flush and topical cooling with ice slush, is relatively slow (Fig. 2). In a pig model of multi-organ procurement, average kidney temperature decreased 1.3°C/min with a rebound effect after the initial *in situ* cold-flush (1). In the clinical setting, average temperatures at the completion of donor nephrectomy measured 19±4°C in donation after brain death (DBD) and 23±4°C in DCD (2). Liver core temperature dropped below 20°C (surface temperature 5°C) after initiating the cold flush and slowly decreased to 8±2°C at the end of donor hepatectomy (3-5). Whether transfer to ice slush on the back-table, for inspection and preparation for preservation, changes kidney temperature is unknown but liver surface temperature increased to 15°C during donor back-table work with core temperatures of 0°C–4°C only reached several hours after storage on ice (3-5). The kidney and liver rewarm on the recipient back-table despite immersion in an ice-cold solution. A temperature increase from 1.6±1.5°C (range 0.7°C–8.4°C) after cold storage to 4.2±2.8°C (range 0.4°C–13.8°C) at the end of back-table preparation has been observed for living donor kidneys (6). Liver surface temperatures of 14°C have been measured during recipient back-table work (5). During implantation, temperature rises, notwithstanding the surgeons' efforts to keep the organ cool, for example by wrapping it in cold swabs or surface irrigation with ice-cold normal saline (7). Feuillu *et al.* observed parenchymal temperatures of 19°C–33.7°C at the end of kidney

implantation with a mean rewarming rate of 0.48°C/min (7). After living donation, the majority of kidneys described by Kuipers *et al.* had temperatures above 15°C at 30 minutes of implantation (6). Liver surface and core temperatures of 16°C and 17±3°C, respectively, have been measured at the end of implantation (4, 5).

Kidney

Nephrectomy times of 40–50 minutes are reported in deceased donation but vary widely (Table 1). The recovery ischemia during donor nephrectomy can impact short and long-term outcome (Table 1). Osband *et al.* showed that every 5-minute increase in donor nephrectomy time beyond 60 minutes independently correlated with the risk of delayed graft function (DGF) (8). In our recent Eurotransplant registry study, donor nephrectomy time independently predicted death-censored graft failure in DCD but not DBD kidneys. For each 10-minute increase in donor nephrectomy time, the odds of graft failure increased by 5% (9). The magnitude of this effect was comparable to the effect of each additional hour of cold ischemia.

Several studies on nephrectomy time in living donation have been performed, largely driven by fear that laparoscopic techniques would result in more warm ischemic injury compared to open nephrectomy. Laparoscopic removal of the kidney is reported to take 102 seconds longer than open nephrectomy but this has not been shown to influence immediate graft function or long-term graft survival as demonstrated by several randomized trials and a meta-analysis (10). Nevertheless, Nogueira *et al.* showed the odds of early graft dysfunction and DGF increased by 15% for every minute increase in living donor nephrectomy time, despite average living donor nephrectomy times of only 2.92 minutes, and <0.5 minutes longer in the group with impaired early graft function (11). Early graft dysfunction independently decreased death-censored graft survival, but whether living donor nephrectomy time drove this effect was not investigated (11).

While rewarming occurs on the back-table, it is unknown whether donor or recipient back-table time affect post-transplant kidney outcomes (6, 12).

Kidney implantation times around 35 minutes are reported but vary widely and implantation ischemia also impacts on short and long-term outcomes of deceased and living donor grafts (Table 2). Halloran *et al.* were the first to describe implantation time as an independent risk factor for DGF and primary non-function (PNF) (13). The effect on DGF was confirmed by Marzouk *et al.* and in our own cohort (14, 15). In both studies the odds of DGF increased by 5% per minute increase in implantation time. Implantation

time is also associated with histological fibrosis on protocol biopsies and graft function up to 2 years post-transplant (15). The effect on graft survival was demonstrated by two transplant registry studies. A study from the United States showed an independent risk of increased death-censored graft failure and patient death with a functioning graft if implantation time exceeded 30 minutes (16). Our own Eurotransplant study confirmed the effect on death-censored graft failure, with increased odds of 10% per 10-minute increase in implantation time but found no effect on mortality (17).

In living donor kidney transplantation, implantation time also independently increased the risk of poor early graft function. Similar to deceased donor kidneys, the odds of poor early graft function increased by 5% for every additional minute of implantation time (18). This deleterious effect was confirmed by Khan *et al.* who found a 7-fold increased odds of poor early graft function with implantation times exceeding 60 minutes (19). Hellegering *et al.* found a 4-fold increased odds of poor early graft function where the sum of the donor nephrectomy and implantation times was greater than 45 minutes. The latter study also showed a 3-fold increased odds of death-censored graft failure where the cumulative time was over 45 minutes (20). Similarly, Tennankore *et al.* found implantation times longer than 50 minutes, in 10-minute tiers, to be an independent risk factor of death-censored graft failure (16).

Graft susceptibility to ischemia during donor nephrectomy and implantation depends on donor type with more pronounced detrimental effect in DCD compared to DBD kidneys. In the Eurotransplant registry, increasing donor nephrectomy time increased the risk of graft failure only in DCD and not DBD (9). The same registry showed a more pronounced effect of implantation time on graft failure in DCD versus DBD (17). In the United States registry, a higher adjusted relative hazard for graft failure in DCD was found (16). This is likely caused by the additional donor warm ischemia. Indeed, when donor warm ischemia time was added to the model, DCD status was no longer associated with kidney graft failure in our Eurotransplant registry study, while the sum of donor warm ischemia and implantation time was (17). Osband *et al.* found that graft failure within 90 days directly correlated with donor nephrectomy time, and this effect was more pronounced in organs from expanded criteria donors, but no multivariable analysis was done (21). In our study, neither donor criteria (expanded versus standard criteria donors) nor kidney donor risk index modified the effect of implantation time on graft failure (17). There is evidence for a more pronounced effect of implantation time on graft failure in deceased donor kidneys compared to living donor kidneys (16).

Liver

Donor hepatectomy times of around 35-40 minutes are reported but vary widely, and they have a detrimental effect on short and long-term post-transplant outcomes (Table 3). Adelman *et al.* showed an independent correlation between donor hepatectomy time in DBD and early graft function measured by the Model for Early Allograft Function score (22). In our cohort, the risk of early allograft dysfunction was not influenced by donor hepatectomy time (23). However, the odds of ischemic cholangiopathy increased by 19% per 10-minute increase in donor hepatectomy time (23). Our Eurotransplant registry study showed donor hepatectomy time to be an independent predictor of overall graft failure (24). The magnitude of this effect resembled that of each additional hour of cold ischemia (24). In a registry study of DCD livers in the United Kingdom, donor hepatectomy time exceeding 60 minutes independently correlated with PNF, early graft loss, and graft failure (25). The hazards for donor hepatectomy time beyond 60 minutes were higher than these for cold ischemia time exceeding 8 hours for all outcome parameters, and cold ischemia time even failed to correlate with early graft loss when adjusted for donor hepatectomy time.

The relationship between donor or recipient back-table time and post-transplant liver outcomes has not been investigated.

The time taken for liver implantation also affects short and long-term post-transplant outcomes (Table 4). Implantation times of 40-45 minutes until portal reperfusion have been reported, with wide variation (Table 4). In our single-center study, the odds of early allograft dysfunction independently increased by 26% for every 10 additional minutes to portal reperfusion (23). The time between portal and hepatic artery reperfusion increased the odds of early allograft dysfunction by 13% per 10-minute increase (23). In a UNOS registry study, implantation time exceeding 70 minutes, in 10-minute tiers, was one of the factors that most significantly correlated with 90-day mortality (26). Our own Eurotransplant registry study showed an effect on long-term mortality with a 3% increased hazard for every 10-minute increase in implantation time. A similar effect was found for death-censored graft failure which was most pronounced early post-transplant with no evidence of a significant effect beyond 90 days (27).

There is no evidence that the effect of ischemia during donor hepatectomy on ischemic cholangiopathy is more pronounced in DCD versus DBD livers (23). In the Eurotransplant cohort, however, the effect of donor hepatectomy time on death-censored graft failure was more pronounced in DCD than DBD livers. Indeed, the hazard in DCD increased by 14% for every 10-minute increase in donor hepatectomy time while this was only 3% with DBD livers (24). Unlike in kidney, there is no evidence that DCD livers are

more susceptible to implantation ischemia, though this might be related to low numbers of DCD included in the studies (27). In the Eurotransplant cohort study investigating donor hepatectomy time, a higher donor risk index was an additional independent risk factor for death-censored graft failure (24). Buchholz *et al.* showed a cumulative effect of implantation time and graft quality, as assessed by the donor risk index (28).

Strategies to protect the graft

Together, the effect on graft failure in different cohorts and various sensitivity analyses indicate that the times taken for donor nephrectomy, donor hepatectomy, and implantation are risk factors for short and long-term post-transplant outcome that nevertheless have received little attention. Many registries do not collect these times and UNOS stopped registering implantation time in 2015 (16). To our knowledge, none of the large transplant registries collect information on back-table time, although this might be a valuable variable to investigate (12).

Opportunities to improve graft outcomes can be categorized into 4 groups: (a) reducing the duration of these ischemic phases, (b) optimizing cooling during ischemia, (c) developing downstream strategies to reduce the impact of ischemia, and (d) avoiding ischemia altogether.

The first strategy, reducing the length of these phases, is not a straightforward approach. Indeed, organ retrieval and implantation ought to be done swiftly to reduce ischemia, but at the same time they need to be done diligently to reduce the risk of unintended organ injury, as well as vascular and other complications. The independent effects of these phases on post-transplant outcomes underline the importance of specific training in procurement and transplant surgery and the performance of a critical number of procedures under supervision before becoming independent (29).

The finding that surgical experience (fellow versus attending surgeon) independently associated with longer donor hepatectomy and donor nephrectomy times illustrates this (22). Appropriate training is particularly important in DCD procedures as DCD organs have been shown to suffer more surgical injury during procurement than DBD organs (29-31), donor hepatectomy and nephrectomy times are longer, and DCD livers and kidneys are more susceptible to the recovery ischemia.

The surgical technique itself might provide a strategy to reduce recovery and implantation ischemia time. Indeed, when no liver hilar dissection is performed before the cold flush in the donor (in DCD), or if this dissection is reduced to a minimum (as can be the case in DBD), additional time consuming and

potentially hazardous hilar dissection in the cold phase can be avoided by staying away from the liver pedicle either by *en bloc* removal of the liver with the pancreas or by dividing the pancreatic head if the pancreas is not to be procured (33, 34). A systematic review concluded that *en bloc* removal of abdominal organs with separation during cold back-table dissection, particularly if pancreas or intestine is included, results in quicker procedures with lower liver PNF rates, though it is unclear whether donor hepatectomy time itself is shortened or just the overall duration of donor surgery (34). *En bloc* procurement will likely increase donor back-table time as a consequence, but whether this affects outcome still needs to be investigated. In Eurotransplant, donor hepatectomy and nephrectomy times are longer in DCD than DBD (9, 24). This is likely explained by the DCD-procurement technique where all dissection happens after cold flush. In addition, dual perfusion of aorta and portal vein, when used, adds time to the procurement (34). Normothermic regional perfusion allows organ mobilization to occur under less duress, prior to organ cooling, because the supply of oxygenated blood is restored to the (thoraco)abdominal organs (35). Whether this reduces the impact of donor hepatectomy and nephrectomy time is not known.

Implantation time should be kept as short as possible as well where both experience and technique play a role. Indeed, more experienced surgeons have the shortest kidney implantation times, though similar graft function and one-year survival was found for all experience levels, perhaps related to selection bias (more difficult procedures or recipients with more comorbidities in the most experienced group) in this observational study (32). Real-time monitoring of implantation time during teaching cases is important to ensure appropriate training opportunities while avoiding lengthy implantations that will be detrimental to the graft. In liver transplantation, shorter implantation times have been reported when the recipient vena cava is preserved compared to classical caval replacement (mean difference of 11.50 minutes) (36).

A second strategy involves optimization of cooling efforts. The use of abundant ice slush with immersion of as much of the organ as possible during donor and recipient back-table work is important. Also, donor back-table work should be limited to separation of the bloc, inspection, vascular/biliary flush, and packing, to prioritize organ cooling over extensive back-table work that best takes place at the recipient center when core-cooling has taken place (37). Use of an ice bag during implantation has been compared to placebo in a study involving 134 kidney transplantations. With this ice bag technique, the kidney is introduced into a plastic bag with ice with a small hole made near the hilum through which the renal artery and vein are passed. The risk of DGF did not differ between the two groups (38). In a second, matched case-control design study of 46 kidney transplants, implantation with or without ice bag was compared (39). Less DGF and a higher glomerular filtration rate on day 14 was observed in the cooling group, accompanied by a decrease in gene expression of some kidney injury markers. Nevertheless,

surface cooling might be insufficient, especially for large organs such as the liver. Other approaches such as flushing the kidney and liver during implantation with cold preservation fluid might reduce rewarming, though perhaps at the risk of recipient hypothermia.

The third strategy is the development of therapies for downstream injury processes that take place during ischemia and upon reperfusion. Briefly, these derangements and potential targets include, but are not limited to, the cellular metabolic disturbances upon local ischemia leading to parenchymal cell death, the profound inflammatory immune response with direct and indirect cytotoxic mechanisms, up to (epi-)genome modifications inducing long-term changes (40, 41). To our knowledge, no therapeutic strategy addressing these downstream processes has entered the clinical arena.

The fourth strategy, ischemia-free transplantation, combines adapted surgical techniques and organ perfusion to completely avoid ischemia. This innovative strategy has been described by He *et al.* who's team accomplished 28 ischemia-free DBD-liver transplants and one ischemia-free DBD-kidney transplant (42, 43). The technique is fairly complex; wider implementation would likely require adaptations, and, ideally, the ischemia-free retrieval of all (abdominal) organs. Still, the prospects of ischemia-free transplantation are attractive (44). Combining this methodology with normothermic regional perfusion might allow to transfer the technique to DCD donation, therefore avoiding all but donor warm ischemia time.

In conclusion, several large cohort studies have shown the detrimental effects of ischemia occurring during donor hepatectomy, donor nephrectomy and implantation on post-transplant outcomes. Standardized reporting in national and international registries would allow donor nephrectomy and hepatectomy as well as implantation times to be used for outcomes research and quality improvement to advance the field.

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Disclosure

The authors have no conflicts of interest to declare as described by the *American Journal of Transplantation*.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Figure legends

Fig. 1: The different ischemic phases during organ transplantation.

In donation after brain death (DBD), oxygen deprivation and ischemia start at aortic cross-clamp and continue during graft removal, graft transportation (unless the organ undergoes some form of oxygenated organ perfusion), and implantation until reperfusion is achieved in the recipient. In donation after circulatory death (DCD), the situation is more complex; ischemia definitely takes place at the time of circulatory arrest, but hypoxemia starts when hemodynamic instability is present during the agonal phase of the dying process.

The time taken for organ removal, and during which organs are exposed to recovery ischemia, is the time from the start of *in situ* cold perfusion until transfer to ice slush on the back-table at the donor hospital. This is referred to as donor hepatectomy time for the liver and donor nephrectomy time for kidney. Donor back-table (BT) time is the time it takes to prepare the organ for packaging in the icebox or placement on a perfusion device. Recipient back-table time is taken from the moment the organ is placed in ice slush to be prepared for implantation until the organ is positioned inside the recipient body, re-packed, or replaced on the perfusion device. During back-table work, organs are exposed to back-table ischemia. Implantation time is the time from removal of the organ out of ice when the anastomoses start until reperfusion in the recipient.

Fig. 2: Temperature changes of the kidney graft from graft procurement to implantation. Temperature estimates are based on studies that measured kidney graft temperature during the donor procedure, cold preservation, and transplantation (2, 7, 45).

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Tables

Table 1 Overview of studies investigating the independent effect of donor nephrectomy time on short and long-term outcomes after kidney transplantation, organized by donor type and publication date

Author & Study details	Donor nephrectomy time		
	Length (min)	Independent effect short-term outcome	Independent effect long-term outcome
Deceased donor kidneys			
Osband 2016 (21) Single center, n=576 (520 DBD, 56 DCD)	44.7 [16.9; 14-123] <60 min: n=493 >60 min: n=83	For times>60 minutes; per 5 min increase PNF: aOR: 1.19 (95% CI 0.96-1.49) DGF: aOR: 1.19 (95% CI 1.02-1.39)	For times>60 minutes; per 5 min increase Death-censored graft failure: aHR: 0.66 (95% CI 0.32-1.38)
Heylen 2020 (9) Registry, n=13914 (12855 DBD, 1059 DCD)	51 (39-65) DBD: 50 (39-64) DCD: 57 (43-78)	-	Graft failure, per 10 min increase: <i>in DBD:</i> aHR: 1.01 (95% CI 0.98-1.04) <i>in DCD:</i> aHR: 1.05 (95% CI 1.01-1.09)
Living donor kidneys			
Nogueria 2009 (11) Single center, n=946	2.92 [1.51]	Poor EGF: aOR: 1.15 (95% CI 1.02-1.28) per 1 minute increase	-

median (IQR); mean [SD and/or range]

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; EGF, early graft function (composite endpoint as either DGF (need for dialysis on POD1-7) or SGF (serum creatinine ≥ 3.0 mg/dL at POD 5 without need for dialysis on POD 1-7) ; IQR, interquartile range; n.a., not available; POD, postoperative day; PNF, primary non-function; SD, standard deviation; SGF, slow graft function

This overview is limited to papers mentioned in the manuscript and should be considered as non-exhaustive as no systematic search was carried out.

Table 2 Overview of studies investigating the independent effect of implantation time on short and long-term outcomes after kidney transplantation, organized by donor type and publication date

Author & Study details	Kidney implantation time		
	Length (min)	Independent effect short-term outcome	Independent effect long-term outcome
Deceased donor kidneys			
Halloran 1988 (13) Multicenter, n=207 (DBD)	<i>PNF 47.5 [1.5]</i> <i>DGF 46.3 [1.5]</i> <i>EGF: 41.5 [1.5]</i>	<i>Versus EGF, per 1 minute increase</i> DGF: MVRC -0.049 (SE 0.018) PNF: MVRC -0.053 (SE 0.019)	-
Marzouk 2013 (14) Single center, n=298	30 (24-45)	<i>per 1 minute increase</i> DGF: aOR 1.04 (95% CI 1.02-1.06)	-
Heylen 2015 (15) Single center, n=699 (DBD)	34 (30-40)	<i>per 1 minute increase</i> DGF: aOR 1.05 (95% CI 1.02-1.07) eGFR (90 days): MVRC -0.11	eGFR 1y: MVRC -0.09 eGFR 2y: MVRC -0.11 eGFR 3y: MVRC -0.09 Interstitial fibrosis 1y: aOR 1.05 (1.02-1.08) Interstitial fibrosis 2y: aOR 1.06 (1.02-1.12)
Tennankore 2015 (16) Registry, n=131677 (71891 DBD, 9199 DCD, 50587 living donors)	35 (27-45) for overall population	-	<i>Versus reference category (10 to <20 min)</i> Death-censored graft failure, DBD and DCD: <i>30-<40 min:</i> aHR: 1.23 (95% CI 1.08-1.39) <i>40-<50 min:</i> aHR: 1.23(95% CI 1.08-1.39) <i>50-<60 min:</i> aHR: 1.28 (95% CI 1.12-1.46)

			≥ 60 min: aHR:1.34 (95% CI 1.18-1.52) Death-censored graft failure, DCD only: $50 < 60$ min: aHR: 1.49 (95% CI 1.07-2.08) ≥ 60 min: aHR: 1.40 (95% CI 1.01-1.93)
Heylen 2016 (17) Registry, n=13964 (12806 DBD, 1158 DCD)	36 (29-45)	-	<i>per 10-minute increase</i> Death-censored graft failure: aHR: 1.10 (95% CI 1.06-1.14) Patient death: aHR: 1.00 (95% CI 0.97-1.02)

Living donor kidneys			
Brennan 2004 (18) Single center, n=469 (open & laparoscopic)	SGF: 35.5 [12.0] DGF 33.7 [7.0] EGF: 30.9 [8.2]	<i>per 1 minute increase</i> Poor EGF: aOR 1.05 (95% CI 1.02-1.08)	-
Hellegering 2012 (20) Single center, n=472 (open & laparoscopic)	29.8 [n.a.]	<i>Sum of donor nephrectomy and implantation time >45 min versus ≤ 45 min</i> Poor EGF: aOR 4.25 (95% CI 1.91-9.47)	<i>Sum of donor nephrectomy and implantation time >45 min compared to ≤ 45 min</i> Death-censored graft failure: aHR: 3.16 (95% CI 1.20-8.32)
Tennankore 2015 (16) Registry, n=131677 (71891 DBD, 9199 DCD, 50587 living donors)	35 (27-45) for overall population	-	<i>Versus reference category (10 to <20 min)</i> Death-censored graft failure: $50 < 60$ min: aHR: 1.22 (95% CI 1.01-1.44) ≥ 60 min: aHR:1.17 (95% CI 1.00-1.37)
Khan 2019 ^a (19)	<45 min: n=55	<i>Versus <45 minutes</i>	-

Single center, n=102 (90 living donors, 12 DBD)	45-60 min: n=33 >60 min: n=14	Poor EGF: >60 min: aOR 7.14 (95% CI 2.35-12.50)	
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median (IQR); mean [SD and/or range]

^a, deceased and living donor kidneys were assessed with a majority of living donor kidneys and therefore listed in that section.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; EGF, early graft function (composite endpoint as either DGF (need for dialysis on POD1-7) or SGF (serum creatinine ≥ 3.0 mg/dL at POD 5 without need for dialysis on POD 1-7); eGFR, estimated glomerular filtration rate; IQR, interquartile range; MVRC, multivariable regression coefficient; n.a., not available; POD, postoperative day; PNF, primary non-function; SD, standard deviation; SE, standard error; SGF, slow graft function

Note this overview is limited to papers mentioned in the manuscript and should be considered as non-exhaustive as no systematic search was carried out.

Table 3 Overview of studies investigating the effect of donor hepatectomy time on short and long-term outcomes after deceased donor liver transplantation, organized by publication date

Author & Study details	Donor hepatectomy time		
	Length (min)	Independent effect short-term outcome	Independent effect long-term outcome
Adelmann 2018 (22) Single center, n=292 (DBD)	40 (32-51)	<i>per 1 minute increase</i> MEAF: MVRC 0.021 (95% CI 0.007–0.035)	-
Jochmans 2019 (24) Registry, n=12974 (12513 DBD, 461 DCD)	41 (32-52) DBD: 40 (32-52) DCD: 50 (35-68)	-	<i>per 10-minute increase</i> Graft failure: aHR: 1.03 (95% CI: 1.02 to 1.05) Death-censored graft failure: aHR: 1.04 (95% CI: 1.01 to 1.06) Patient death: aHR: 1.03 (95% CI: 1.01 to 1.05)
Gilbo 2020 (23) Single center, n=917 (793 DBD, 124 DCD)	35 (26-46) DBD: 35 (26-47) DCD: 34 (28-41)	<i>per 10-minute increase</i> EAD: aOR: 1.04 (95% CI: 0.93-1.16) IC: aHR: 1.19 (95% CI: 1.04-1.35)	-
Farid 2019 (25) Registry, n=1112 (DCD)	35 (26.5-47)	<i>>60 minutes versus <30 minutes</i> PNF: aHR: 3.67 (95% CI, 1.36– 9.87) Graft failure (<90 days): aHR: 3.29 (95% CI 1.33-8.10)	<i>>60 minutes versus <30 minutes</i> Graft failure: aHR: 1.95 (95% CI 1.24-3.07)

median (IQR); mean [SD and/or range]

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; IC, ischemic cholangiopathy; IQR, interquartile range; n.a. not available; MEAF, model of early allograft function; MVRC, multivariable regression coefficient; PNF, primary non-function; SD, standard deviation

Note this overview is limited to papers mentioned in the manuscript and should be considered as non-exhaustive as no systematic search was carried out.

Table 4 Overview of studies investigating the independent effect of implantation time on short and long-term outcomes after liver transplantation, organized by publication date

Author & Study details	Liver implantation time		
	Length (min)	Independent effect short-term outcome	Independent effect long-term outcome
Rana 2008 (26) Registry, n=21673 (DBD and DCD, no further details)	n.a.	<i>Versus 30-60 minutes</i> Patient death (<90 days)*: <i>70-80 min:</i> aOR: 1.5 (95% CI 1.06-2.19) <i>80-90 min:</i> aOR: 1.8 (95% CI 1.09-3.00) <i>>90 min:</i> aOR: 2.3 (95% CI 1.58-3.41)	-
Jochmans 2018 (27) Registry, n=5223 (5015 DBD, 208 DCD)	41 (34-51)	-	<i>per 10-minute increase</i> Graft failure: aHR: 1.04 (95% CI 1.01-1.07) Death-censored graft failure: aHR: 1.04 (95% CI 1.01-1.09) Patient death: aHR: 1.03 (95% CI 1.00-1.06)
Buchholz 2018 (28) Single center, n=678 (512 DBD, 163, DCD, 3 n.a.)	n.a.	<i>Versus ≤34 minutes</i> EAD: ≥44 minutes: 3.31 (95% CI 1.93-5.68) Acute kidney injury: ≥44 min: 2.37 (95% CI 1.43-3.93)	<i>Versus ≤34 minutes</i> Graft failure: ≥44 minutes: aHR: 2.39 (95% CI 1.19-4.77) <i>Versus ≥44 minutes and DRI <2.3</i> Graft failure: ≥44 minutes and DRI >2.3:

			aHR: 3.37 (95% CI 1.42-7.99)
Gilbo 2020 (23) Single center, n=917 (793 DBD, 124 DCD)	80 (66-95) PV time ^a : 45 (39-56) HA time ^b : 33 (22-44)	<i>per 10-minute increase</i> EAD: aOR: 1.15 (95% CI: 1.07-1.23) <i>PV time: aOR: 1.26 (95% CI: 1.12-1.42)</i> <i>HA time: aOR: 1.13 (95% CI: 1.04-1.22)</i> IC: aHR: 1.03 (95% CI: 0.96-1.11) <i>PV time: aHR: 0.98 (95% CI: 0.84-1.14)</i> <i>HA time: aHR: 1.06 (95% CI: 0.97-1.15)</i>	-

median (IQR); mean [SD and/or range]

^a time between liver out of ice and PV. reperfusion

^b time between PV and HA. reperfusion

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; DRI, donor risk index; EAD, early allograft dysfunction; HA, hepatic artery; IC, ischemic cholangiopathy; IQR, interquartile range; n.a., not available; PNF, primary non-function; PV, portal vein; SD, standard deviation

Note this overview is limited to papers mentioned in the manuscript and should be considered as non-exhaustive as no systematic search was carried out.

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