Logistical Factors influencing Cold Ischaemia Times In Deceased Donor Kidney Transplants

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Abbreviations:

CIT: cold ischaemia time

DD: deceased donor

DCD: donation after circulatory death

DBD: donation after brain death

DGF: delayed graft function

H&I: Histocompatibility and Immunogenetics

NHSBT: National Health Service Blood and Transplant

XM: crossmatch

pXM: prospective crossmatch

vXM: virtual crossmatch

SN-OD: Specialist nurses in organ donation

DO: duty office

Abstract:

Background: Prolonged cold ischaemia time (CIT) is associated with a significant risk of short and long-term graft failure in deceased donor (DD) kidney transplants across the world. The aim of this prospective longitudinal study was to determine the importance of logistical factors on CIT.

Method: Data on 1763 transplants were collected prospectively over 14 months from personnel in 16 transplant centres, 19 Histocompatibility and Immunogenetics laboratories, transport providers and NHS Blood and Transplant (NHSBT).

Results: The overall mean CIT was 13.8 hours, with significant centre variation ($p<0.0001$). Factors that significantly reduced CIT were donation following circulatory death (DCD)($p=0.03$), shorter transport time ($p=0.0002$), use of virtual crossmatch $p<0.0001$) and use of donor blood for pre-transplant crossmatch ($p<0.0001$). CIT for transplants that went ahead with a virtual crossmatch was 3 hours shorter than those requiring a pre-transplant crossmatch ($p<0.0001$). There was a mean delay of 3 hours in starting transplants despite organ, recipient and pre-transplant XM result being ready, suggesting that theatre access contributes significantly to increased CIT.

Discussion: This study identifies logistical factors relating to donor, transport, crossmatching, recipient and theatre that impact significantly on CIT in DD renal transplantation, some of which are modifiable; attention should be focussed on addressing all of these.

Introduction

Delayed graft function (DGF), which can be defined as the requirement for dialysis in the first 7 days post-transplant, occurs in a significant number of deceased donor renal transplants, cited as between 25 and 50% [1], and is associated with a significantly increased risk of graft loss over the years following transplantation, higher serum creatinine at one year, and an increased risk of acute rejection [2]. Risk factors for DGF include cold ischaemia time (CIT), donor factors such as age and serum creatinine, recipient factors such as body mass index, immunological and logistical factors [3]. Of these, prolonged CIT has been shown to be the most significant individual factor in predicting delayed graft function: Irish et al reported that for every hour increased CIT there was a 4% increased risk of DGF [4]. Cold ischaemia time is defined as the time from commencement of cold perfusion at the time of donor surgery to the removal of the kidney from ice in the recipient centre, and is affected by a complex logistical pathway that includes kidney allocation, transport, crossmatching, preparation of the recipient and access to theatre.

Kidneys that are particularly susceptible to ischaemic damage and DGF are those from deceased donors following circulatory death (DCD), and extended criteria donors (older (>60 years) donors and those with co-morbidities, eg cardiovascular disease) [5]. With increasing numbers of patients waiting for transplantation, more such organs are accepted and thus CIT will remain an important consideration in deceased donor transplantation [6,7]. We prospectively studied the impact of individual logistical factors on CIT, relating to events from the time of kidney retrieval at the donor hospital to kidney being removed from

ice in the recipient centre (Figure 1). Whilst logistical details vary between nations and organ sharing schemes, our findings are worthy of careful reflection internationally.

Results

General Demographics

Data include information for 1763 single/double/en-bloc kidney only and SPK transplants from across the United Kingdom. Of those, 1586 (90%) were kidney only and 177 (10%) SPK transplants. Fifty-five of the 1586 kidney only transplants were double and 4 were en-bloc kidney transplants. DCD kidneys constituted more than a third (41%) of the transplants and the majority of kidneys (64%) were shipped between centres. 43 (2%) kidneys were reallocated: 32 were reallocated locally and 11 were reallocated to a different transplant centre.

Cold ischaemia times

The overall mean CIT for kidney transplants in all transplant centres was 13.8 hours (SD 4.5, IQR 10.7-16.4). The shortest recorded CIT was 3.7 hours and the longest was 33.1 hours.

There was significant centre variation in mean CIT across the UK transplant centres ranging between the shortest of 12.0 hours and the longest of 20.4 hours in the 22 centres ($F=10.060$, $p<0.0001$), as shown in Figure 2.

The most significant factor affecting CIT overall was the adoption of a virtual crossmatch policy. Transplants that required a prospective pre-transplant crossmatch had a CIT that was 3 hours longer than those where the crossmatch test was omitted and proceeded directly to transplant based on a negative virtual crossmatch (Figure 3, $p<0.0001$). There was significant centre variation in the number of transplants performed using vXM; indeed at the time of the study two centres had not adopted a virtual crossmatch policy ($P<0.0001$). Due to the key role played by the type of crossmatch performed and the fact that the kidney pathway diverges depending on whether the transplant requires a pre-transplant cross match or not, the analysis was performed separately for virtual crossmatch (vXM) and pre-transplant crossmatch (pXM) groups.

If a pre-transplant crossmatch is required this can be performed using donor peripheral blood obtained pre-retrieval, or lymph node and spleen that are taken at time of retrieval and accompany the organs to the recipient centre. We sought to determine whether there was variation in practice with regard to use of donor tissue for pXM, as this was likely to significantly alter the timing of availability of the XM result. There were significant differences in laboratory practice, with one laboratory performing approximately 89% pXM on peripheral blood, whilst other laboratories were dependent on the arrival of lymph nodes and spleen in all cases (Figure 4).

The factors that were included in a univariate analysis for both vXM and pXM groups are outlined in Table 1 (categorical) and Table 2 (continuous). These

include factors pertaining to each stage of the kidney journey from donor to recipient, and key timelines of the process.

Factors affecting CIT in transplants requiring pre-transplant crossmatch test (univariate analysis)

In the pre-transplant crossmatch group, several factors contributed significantly to CIT in univariate analysis: CIT was significantly shorter in DCD transplants than DBD ($p=0.0003$); kidneys that were transplanted locally had a shorter CIT than those that were exported ($p<0.0001$), and CIT was prolonged if kidneys were reallocated either locally or to a second centre ($p=0.0007$). Importantly, if the prospective crossmatch was performed using donor peripheral blood obtained prior to start of retrieval, rather than donor lymph nodes and spleen obtained at retrieval and transported with the organs, CIT was significantly reduced ($p<0.0001$). Similarly, if stored recipient blood was available for crossmatching purposes, this resulted in a significant reduction in CIT ($p<0.0001$). Continuous variables that were found to contribute to CIT in the prospective crossmatch group were transport times, time taken from *in situ* cold perfusion to the kidney boxed ready for transport, time between the offer made and the kidney accepted by the recipient centre, and time to obtain the crossmatch result. Once the kidney had arrived and pXM result known, any further delay in proceeding with the transplant was documented, and was found to have a significant impact on CIT.

Factors affecting CIT in transplants undertaken using virtual crossmatch (univariate analysis)

Significant factors in univariate analysis were donor type (DBD/DCD) (p=0.01), and whether the kidney was allocated locally or imported from another region (p=0.04). In the small number of kidneys that were reallocated, this had a significantly detrimental impact on CIT (p<0.0001). Requirement for recipient haemodialysis pre-transplant also had a significant impact (p=0.003). Continuous factors that were relevant included timing from cold perfusion to kidney boxed ready for transport, offer accepted to contacting the recipient, timing of kidney collection and its transport.

Multivariate analysis of factors affecting CIT

All factors that were significant in univariate analyses were considered in multivariate modelling, and factors that remained significant are shown in Table 3. Key findings in the prospective crossmatch group are shown in Table 3a: if peripheral blood is used for pXM, CIT is reduced by more than 3 hours. Factors that led to an increased CIT are travel times (adding between 1.5 and 2.3 hours), or kidney reallocation (+2.6 hours). In addition, once the kidney had arrived and the pXM result was known, a further delay in start of surgery had a significant detrimental impact on CIT. This was also significant in the context of the vXM group (Table 3b), leading to a significant delay in commencement of surgery and thus increasing CIT. Other factors that remained significant in the vXM group were the patient requiring haemodialysis prior to transplant, travel time and kidney reallocation.

Discussion

Cold ischaemia time is one of the few modifiable factors that have been identified as a significant risk factor for delayed graft function, with long term implications for graft survival in deceased donor renal transplants [2,8,9,10]. It is likely that, in the current era of accepting kidneys from extended criteria donors, and DCD donors, CIT will continue to play a significant role, and should be minimized, as evidenced by the experience of the Eurotransplant Senior program[11].

We have examined logistical factors that contribute to CIT in the context of national (DBD) and regional (DCD) allocation of DCD kidneys within the United Kingdom. Organ retrieval, transport and implantation logistics vary between countries and organ sharing networks, but, studies examining these are lacking, despite a clear need for such investigation [12]. Thus we consider the international relevance of factors identified in this study based on current literature available. One regional French study examining the impact of the introduction of a timesheet on CIT in locally and nationally allocated kidneys found that the introduction of such a time sheet alone reduced CIT from 21 hours to 13 hours in a case control study [13]. Another review of factors affecting CIT in Chile highlighted the impact of kidney sharing, reallocation and factors pertaining to HLA typing and crossmatching [14].

The factor that contributed most significantly to CIT was the introduction of a virtual crossmatch policy in patients that were deemed suitable for such: these patients have low immunological risk, with known HLA antibody profile and few unacceptable antigens. This finding requires further interrogation: the

prolonged CIT in patients requiring a pXM may be due to other factors relating to their more complex sensitisation profiles. A study from Cambridge demonstrated that the introduction of such a policy in carefully selected patients could be undertaken safely and leads to an effective reduction in CIT [15,16].

It is likely that lessons can be learned internationally from this finding. In the US, virtual crossmatching is adopted to predict whether or not a kidney should be shipped to a distant centre for transplantation into a sensitized patient, but the pre-transplant crossmatch is still performed on arrival of the kidney at the recipient centre. A review of this policy with the introduction of a virtual crossmatch policy is likely to lead a reduction in CIT, and might be safely introduced [15]. However, introduction of a vXM policy does not always result in reduced CIT, as has been shown recently in a Swiss study: the policy led to improved allocation, reduced workload on the H&I staff, and improved risk stratification for modified immunosuppression, but CIT was the same in both groups[17].

Factors that were common to both pXM and vXM groups were travel time, kidney reallocation and a delay in gaining access to theatre, despite the availability of the crossmatch result and the kidney having arrived at the recipient hospital. When members of staff were interviewed at all transplanting centres across the UK as an early part of this work, the most commonly perceived reason for prolonged CIT was lack of access to theatre, due to competing interests of emergency cases, and availability of anaesthetic and theatre staff. It has been previously shown that more than 50% of kidney transplants are performed overnight and at weekends when there are fewer

operating rooms and less staff coverage (nursing, anaesthetic) [18] and we must implement policy changes that prioritise sufficient theatre access out of hours if we are to continue to strive to minimize CIT and optimise outcomes.

One limitation of the study is the paucity of data relating to transport, recipient and surgical factors. The study relied on information being collected by individual members of the clinical team at the recipient hospital, resulting in approximately 33% data being collected. Formal collection of transport times has now been built into the contract of transport providers. Despite this shortcoming, significant and important factors have been identified, which remain relevant.

With the introduction of novel technologies that aim to improve perfusion and organ preservation, such as machine perfusion and normothermic regional perfusion, static cold storage may become a less commonly adopted technique. However, whilst organs continue to be transported on ice between centres in order to optimize transplant outcomes, CIT remains an important factor [20]. This study has demonstrated specific logistical factors that can be addressed with the potential to minimize CIT further and has international relevance as CIT is recognised as a key factor contributing to delayed graft function.

Method:

Data collection:

Prospective data collection was performed between June 2011 and the end of July 2012. Prior to commencement of the data collection, all UK transplant

centres, specialist nurses for organ donation (SN-ODs) and Histocompatibility and Immunogenetics (H&I) laboratories were visited in order to maximize participation with the study. The study was funded from a research grant from NHS Blood and Transplant (NHSBT), and was approved by the Kidney Advisory Group, which advises NHSBT on all aspects of kidney transplantation within the UK. Staff involved in the data collection included SN-ODs, H&I staff, transport providers, recipient transplant coordinators, transplant surgeons/fellows/specialist registrars, nephrologists, theatre and ward staff and NHSBT.

Data were obtained on deceased donor (DD) kidney only and simultaneous pancreas and kidney (SPK) transplants from 16 of the 22 invited transplant centres (6 centres declined to participate) along with all 19 H&I laboratories (supporting all 22 transplant centres), with the aim of determining whether there are specific areas upon which to focus efforts to reduce cold ischaemia times. CIT was calculated from UK Transplant Registry data held by NHSBT, and was defined as the time from *in situ* cold perfusion in donor at the time of retrieval to the time of removal of kidney from ice for transplantation in recipient. This was available for all transplants performed in all 22 centres.

Factors that were considered to be relevant for this study were agreed with a national multidisciplinary team, including transplant surgeons, H&I scientists, and statisticians. In addition, draft documents were circulated to the heads of transplant centres for their input. Categorical and continuous data were collected along the kidney timeline from the time of organ donation at the donor

hospital to completion of transplantation at recipient hospital on four different data collection forms. We focused on five key logistical areas, namely, donor operation, organ transport, laboratory tests including the match run and the crossmatch, recipient preparation and theatre, as shown in Figure 1. For clarity, the Duty Office (DO) at NHSBT performs the match run once the donor HLA type is known; this is matched to the recipient pool. We examined different factors within each of these key areas to identify those that impacted on CIT.

A national database was set up and data input was done prospectively. Data were checked for errors and each outlier was examined by re-checking them against the original forms as well as with the rest of the data for the corresponding transplant. We excluded transplants that did not proceed despite retrieval of organs, and kidneys that were transplanted with organs other than pancreas. When two kidneys were transplanted in a single recipient (double kidney transplant) the one with the longer CIT was excluded. Data on recipient and theatre times that were inconsistent with the rest of the data and those that had a discrepancy of more than one hour from NHSBT data were excluded (n=52 transplants). Transplants with no vXM or pXM information were excluded. Data cleansing was undertaken prior to the final analysis: 5% of data were selected randomly at regular intervals and each one was checked against the original forms and records to establish excellent quality assurance of the input data. An error rate of <1% was considered acceptable. Data were collected for almost 100% of donor and H&I data for that period, with 37% of transport data, 32% of recipient and 35% of theatre data from the 16 participating centres.

Crossmatch terminology:

Several centres in the UK have adopted selective omission of the pre-transplant crossmatch in potential recipients who are at low immunological risk [16], and this has shown to be safe and effective at reducing CIT [15]. For the purposes of this study, the term 'virtual cross match' is used to describe this policy (vXM).

For clarification in this study, we will use the term pre-transplant crossmatch for those transplants that required full crossmatch testing to be performed prior to start of surgery (pXM), and virtual crossmatch for those in whom the prospective pre-transplant donor crossmatch was omitted and it was safe to proceed without waiting for the crossmatch test to be performed (vXM). The formal crossmatch test was performed retrospectively and there have been no cases of unexpected xm positivity following transplantation.

Statistical Analysis

General demographics of deceased donor kidney and SPK transplantation in the 14-month period included number and type of donors, kidneys, transplants, recipients, allocation and reallocation across the UK transplant centres.. All relevant time intervals were collected in hours. Various time intervals between donor notification and completion of transplant surgery were examined, namely, times of retrieval surgery, transport of organs, donor HLA typing and crossmatching, recipient preparation and transplant theatre. Donor-related categorical data included in the analyses were type of donor (DBD or DCD) and donor tissues used for crossmatching. Transport-related categorical data was

mode of organ transport, H&I-related data were type of crossmatching, types of donor tissues and recipient blood samples used if pre-transplant crossmatch test done, recipient-related categorical factors included mode of recipient travel to the transplant centre, requirement for haemodialysis immediately prior to transplant and requirement for current recipient serum sample for crossmatching. The sole theatre-related categorical factor included was whether the transplant was performed in an emergency or transplant-dedicated theatre.

All data within the study period were included in the univariate analysis. Parametric tests were performed to assess differences in CIT across transplant centres and crossmatch type, variation in crossmatch across transplant centres and variation in practice around the use of donor samples for pre-transplant crossmatch. A general linear model was used to determine the contributions of various factors and time intervals to the cold ischaemia time. Due to missing data, time intervals were analysed categorically. The distribution of each of the time intervals was used to decide appropriate categories. Factors that were found to be significant in the univariate analyses were incorporated in the multivariate modelling. Only significant factors in the multivariate modelling were included in the final model.

P-values of <0.05 were considered significant. All analyses were performed using SPSS version 19, IBM, UK and SAS version 9.4.

Intercept description:

The intercept is the median cold ischaemia time if all other factors are set to zero (the baseline).

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Table 1: Categorical factors included in the univariate analysis for vXM and pXM groups

		Pre-transplant crossmatch		Virtual crossmatch		TOTAL	
Factor	**Level**	**N**	**%**	**N**	**%**	**N**	**%**
Donor type	DBD	703	62	333	52	1036	59
	DCD	424	38	303	48	727	41
Local	No	740	66	390	61	1130	64
	Yes	387	34	246	39	633	36
Reallocated kidney	No / unknown	1104	98	616	97	1720	98
	Yes	23	2	20	3	43	2
Peripheral blood	No	867	79	-		867	79
	Yes	224	21	-		224	21
	Missing	36	-			36	-
Current sample	No	389	35	-		389	35
	Yes	709	65	-		709	65
	Missing	29	-	-		29	-
Recipient mode of travel to hospital	Ambulance	20	6	13	5	33	5
	Air	0	0	4	2	4	1
	Patient's own	286	81	205	77	491	79
	Taxi	46	13	44	17	90	15
	Other	1	<1	0	0	1	<1

	Missing	774	-	370	-	1144	-
Haemodialysis	No	261	71	186	67	447	
Required by	Yes	106	29	91	33	197	
recipient	Missing	760	-	359		1119	

Definitions:

Local: when a kidney, retrieved at one of the hospitals within a defined geographical region, is transplanted at the designated transplant unit for that region

Reallocation: when a kidney, which was initially accepted for transplantation in a particular recipient at a transplant unit, is subsequently allocated to a second recipient at the same or a different hospital

Table 2: Continuous factors included in the univariate analysis for pXM and vXM groups

	Pre-transplant crossmatch (hrs)			Virtual crossmatch (hrs)		
Factor	**N**	**Median**	**IQ Range**	**N**	**Median**	**IQ Range**
Cold perfusion to kidney in ice box	867	1.27	1.02 – 1.55	475	1.28	1.02 – 1.62
Offer accepted to latest of staff in lab, donor sample arrive, or recipient sample arrive	308	9.42	6.20 – 13.00	-		-
Offer accepted to agreement to proceed with a vXM	-	-	-	197	3.00	1.13 – 6.33
Offer accepted to recipient contacted	292	1.80	0.33 – 6.58	222	2.63	0.65 – 6.25
Recipient contacted to recipient arrived	307	2.00	1.33 – 3.00	240	2.00	1.50 – 3.00
Kidney on ice to kidney collected	405	0.93	0.67 – 1.25	201	1.00	0.67 – 1.42
Kidney collected at donor hospital to kidney delivered to recipient centre	426	1.83	1.08 – 3.17	221	2.17	1.33 – 3.42
Matching run complete to pXM result	1100	14.42	10.52 – 19.02	-		-
Matching run complete to	-		-	494	4.43	1.60 –

agreement to proceed with a vXM						9.17
Latest (XM result known, organ delivered) to transplant surgery started	342	3.30	2.28 – 5.17	82	3.82	2.53 – 6.00
Transplant surgery started to kidney out of ice	354	0.90	0.65 – 1.25	264	0.87	0.70 – 1.22

Table 3: Multivariate analysis of factors affecting cold ischaemic time for a) pre-transplant crossmatch group and b) virtual cross match group.

Explanation of 'intercept' is provided in the Methods section

Factor	Level	Estimated change in CIT (hours)	Standard Error	p-value
a) Pre-transplant crossmatch				
Intercept		13.3	0.4	<0.0001
Peripheral blood	No	Baseline		
	Yes	-3.4	0.3	<0.0001
Kidney collected	Less than 2hrs	Baseline		
to	2 – 4hrs	1.5	0.5	0.0007
kidney delivered	More than 4hrs	2.3	0.6	0.0002
	Missing	1.3	0.3	<0.0001
Kidney reallocated	No	Baseline		
	Yes	2.6	0.8	0.0019
Cold perfusion to Kidney on ice	Less than 1hr30	Baseline		
	More than 1hr30	1.1	0.3	0.0004
	Missing	0.7	0.3	0.02
Latest (XM result known, organ	Less than 5hrs	Baseline		
	5 – 9hrs	2.1	0.5	<0.0001

delivered) to	More than 9hrs	5.7	1.0	<0.0001
transplant	Missing	1.5	0.3	<0.0001
surgery started				
b) Virtual crossmatch				
Intercept		8.7	0.7	<0.0001
Donor type	DCD	Baseline		
	DBD	0.8	0.4	0.03
Recipient on HD	No	Baseline		
	Yes	1.3	0.6	0.02
	Missing	1.3	0.4	0.002
Kidney	No	Baseline		
reallocated				
	Yes	5.7	1.0	<0.0001
Kidney collected	Less than 2hrs	Baseline		
to	2 – 4hrs	1.6	0.6	0.01
Kidney delivered	More than 4hrs	2.8	0.9	0.002
	Missing	1.8	0.5	0.0004
Latest (proceed	Less than 5hrs	Baseline		
with vXM, organ	5 – 9hrs	2.7	1.1	0.01
delivered) to	More than 9hrs	7.6	1.7	<0.0001
transplant	Missing	0.8	0.7	0.2
surgery started				

Figure legends:

Figure 1: Logistics of deceased donor transplantation in the United Kingdom (DO-Duty office, XM-crossmatch, HD- haemodialysis)

Figure 2: There was significant variation in CIT between centres across the UK, expressed as box and whisker plot with mean. The shortest mean CIT was 12.00hr and the longest of 20.36hr, compared in all 22 centres ($F=10.060$, $p<0.0001$).

Figure 3: The impact of the cross match type on CIT; transplants that proceeded based on a virtual cross match (omitting the prospective pre-transplant donor crossmatch test) had a median CIT of approximately 3 hours less than those that required a prospective cross match. (t-test, $p<0.0001$).

a) Pre-transplant cross match
b) Virtual cross match

Figure 4: Laboratory variation in practice around use of donor samples for pre-transplant cross match

Figure 1
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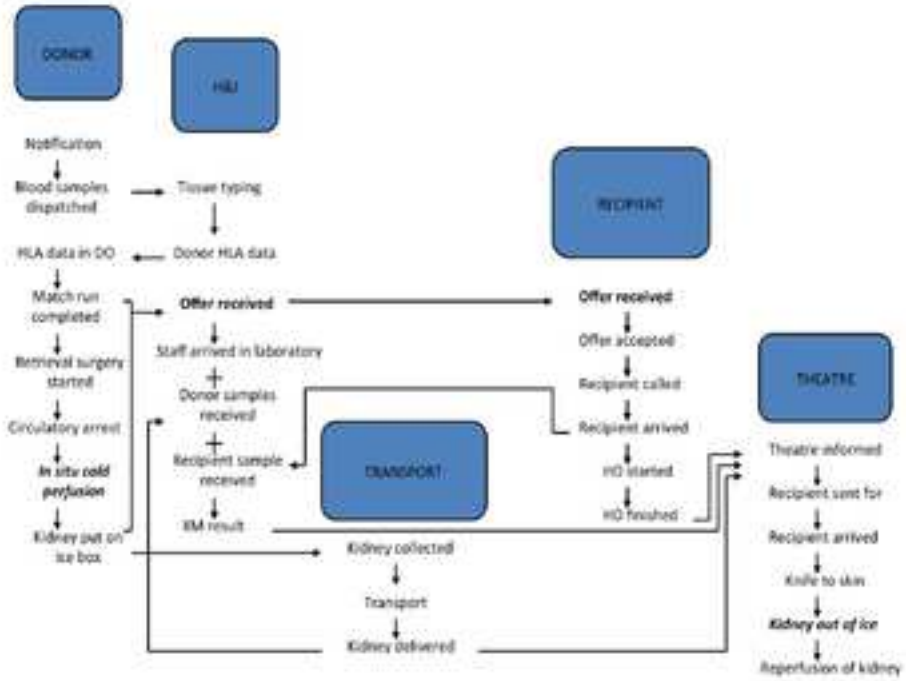

Figure 2
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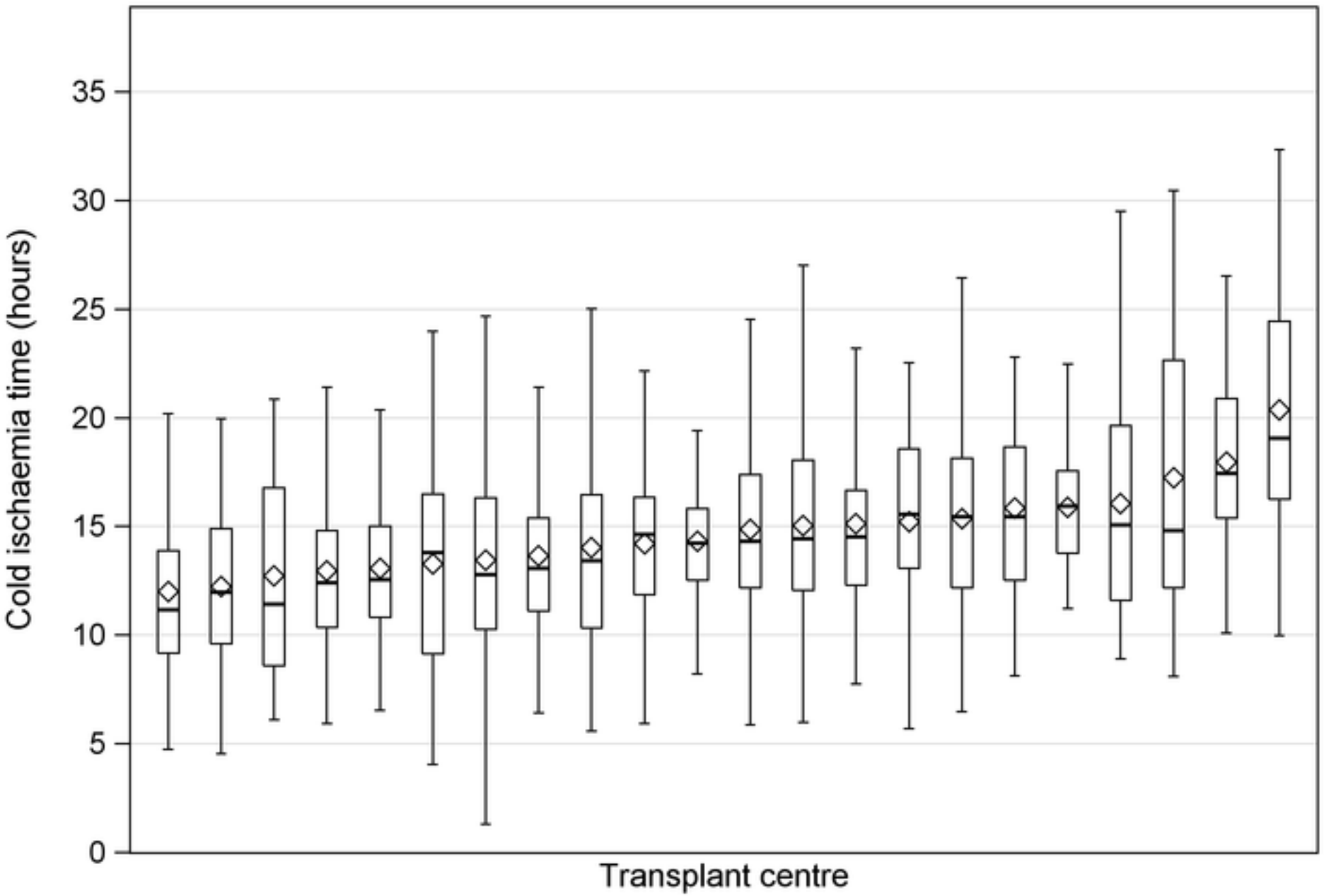

Figure 3
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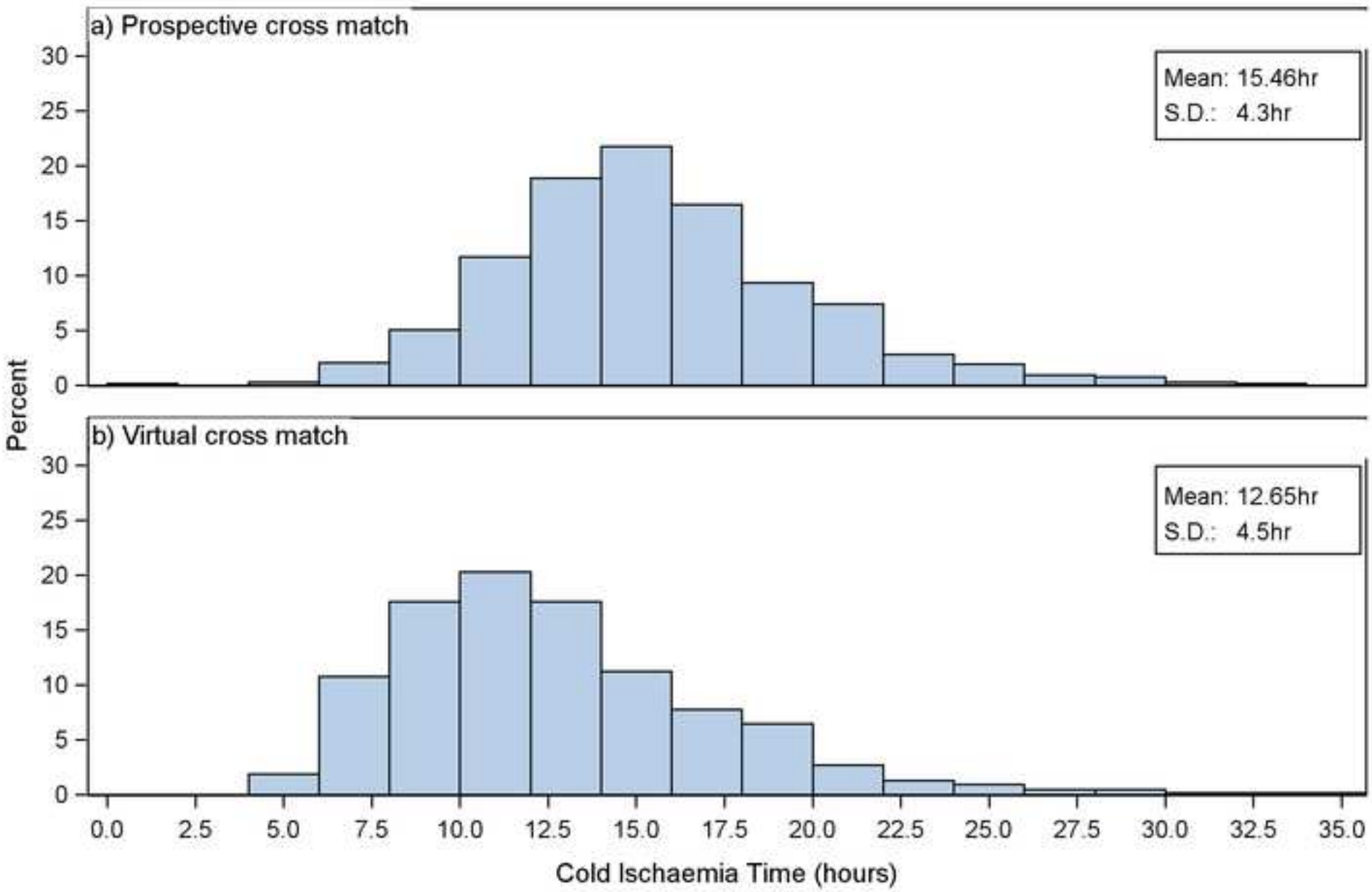

Figure 4
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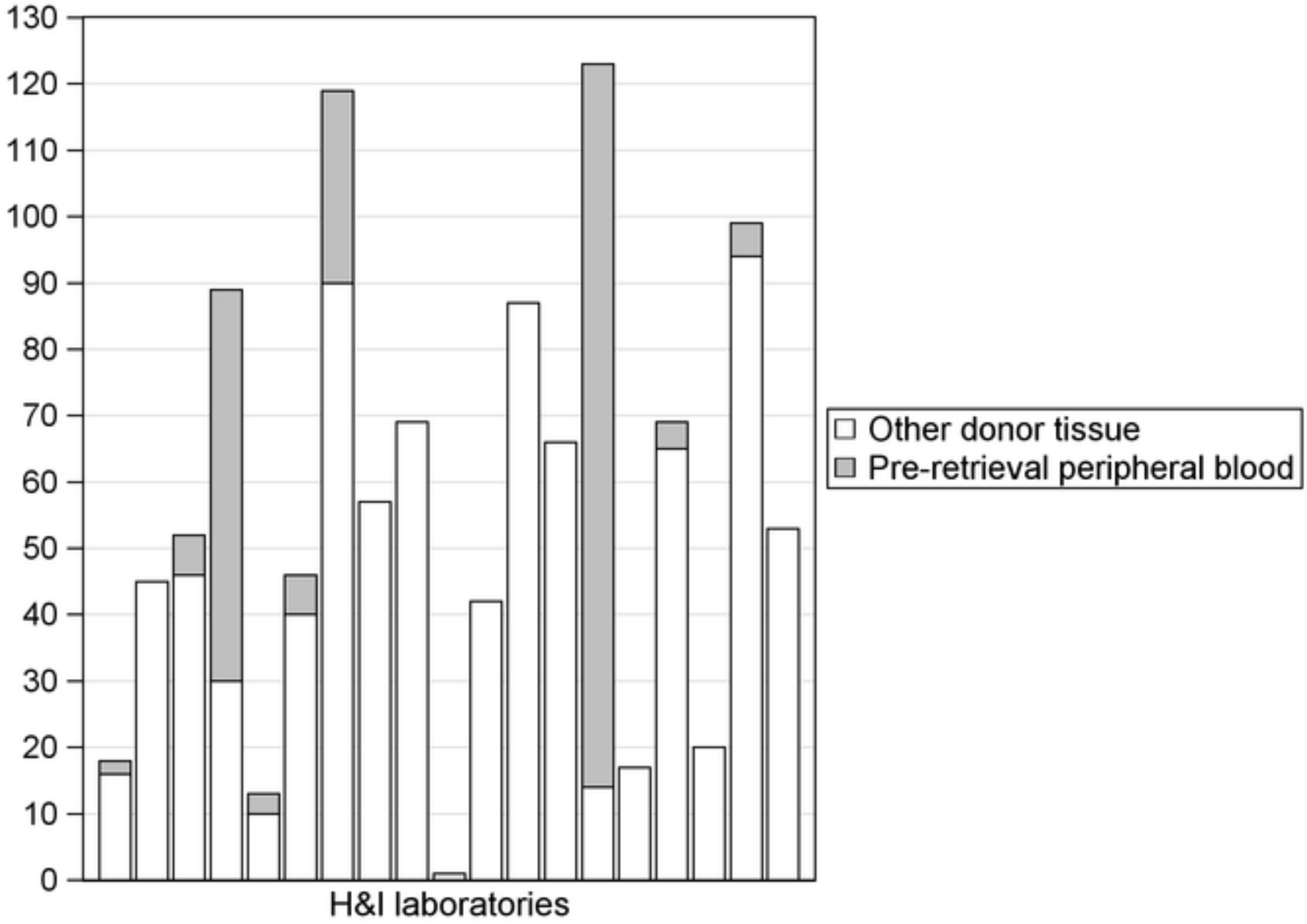

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