Clinical Outcome following heat transplantation of 59 taNRP donor hearts. An International experience:

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Abstract

Background: Heart transplantation is an effective service offering the best recovery in both quality and quantity of life to those trapped by refractory, severe heart failure. However, transplantation is limited by donor organ availability. The reintroduction of non-heart beating heart donation (*DCD donation*) in 2014 offers an uplift in transplant activity by 30%. The DCD donor heart is ischaemic and requires reperfusion. This may occur outside the donor's body (*ex-situ perfusion*) or within it (*thoraco-abdominal normothermic perfusion*: *taNRP*). taNRP is controversial but attracts shorter myocardial ischaemic times and better clinical outcomes.

Method: Outcomes included functional warm ischaemic time, use of mechanical support immediately following surgery, perioperative and long-term actuarial survival and incidence of acute rejection requiring treatment. 59*taNRP* transplants have been included from four major transplant centres worldwide including the UK, USA and Belgium.

Findings: The mean functional total ischaemic time (FTIT) was 16·8minutes. Survival was excellent in this small clinical experience. The median donor heart related survival time was 430days and mean survival 800days. Thirty-day survival (*n=59*), one-year survival (*n=39*) and five-year survival (*n=10*) in terms of donor heart related survival 100% falling to 98·3% when accounting for the intra-operative death following acute aortic dissection at the time of transplantation.

Interpretation: The survival rates of *taNRP* are superior to both DBD (donation after brain death) and direct procurement DCD donors, where the one-year survival is roughly 90%. The difference may in part be related to a shorter FTIT or through a possible selection bias. Therefore, *taNRP* offers an exciting method of organ preservation and procurement. In addition, it offers a tool with which we can increase the total number of transplants being performed and minimise waiting list mortality.

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Introduction

Heart transplantation (*HT*) is reserved for patients with minimal co-morbidity and end-stage heart failure (ESHF), defined as *NHYA III/ IV* which is refractory to medical treatment and is the last bastion for these patients. It offers them a greatly improved prognosis and quality of life (QoL). However, transplantation is limited by donor organ availability. Currently, in the UK there is an estimated waiting list mortality of 35%.[1] This serious problem is related to an imbalance in demand and supply of usable donor hearts. Various approaches to improve heart transplant activity have included Ex-Situ Perfusion Machines (*Organ Care System (OCS) developed by Transmedics*) of heart beating donor hearts in an attempt to expand the donor pool and improve utilisation, the introduction of 'opt-out' for organ donation as well as the reintroduction of donation after circulatory determination of death (DCD) donors.[2]

Most hearts donated for transplantation are acquired from donation after brain death (*heart beating donors or more precisely after the determination of brainstem death*).[1,3] In recent years the development of DCD has increased the size of the donor organ pool and it is estimated that DCD could increase the number of transplantations performed by 30%.[4] Data from 20/21 in the UK shows that DCD transplantations made up only 12% of total cardiac transplantations. However, in the Royal Papworth Hospital, DCD transplantation makes up 30% of the total number of heart transplants.[2] Similarly, data from the US shows that in 20/21, DCD made up 5·4% of transplants [5], however it has been estimated that DCD could increase the donor pool by up to 30%.[6]

In DCD donors, death is confirmed once flow to the brain has ceased for 5 minutes (*cardio-respiratory arrest*), confirming permanent cessation of circulation. These ischaemic DCD hearts are then either procured and reperfused outside the donor's body (*ex-situ reperfusion*) on the OCS or reperfused with in the donor's body by *in-situ* reperfusion by limited thoraco-abdominal normo-thermic reperfusion (*taNRP*). Direct procurement followed by mounting of the DCD heart onto an ex-situ perfusion machine takes time, further prolonging the donor heart FTIT. Myocardial ischaemia is probably the main obstacle in DCD organ procurement. During warm ischaemia the heart is active and depletes its intracellular energy stores rapidly. The mechanisms of this ischaemic injury (and subsequent reperfusion) have been well described elsewhere.[7]

In order to minimise the ischaemic time, the heart may be perfused in-situ. This is known as Thoraco-abdominal normothermic regional perfusion. The aortic arch arteries are occluded to prevent cerebral blood flow. The systemic venous and arterial systems are cannulated and restoration of thoraco-abdominal flow leads to prompt termination of intra-thoracic and abdominal organ ischaemia. After 20 minutes of machine perfusion, heart function is sufficiently recovered to permit weaning off *taNRP*. Donor heart function can be assessed in this, now heart beating donor. *taNRP* significantly shortens cardiac ischaemic time and reverses the risk of permanent ischaemic metabolic damage. Results from NRP (normothermic regional perfusion) in liver

transplantation have shown significant reduction of biliary strictures when compared to the standard rapid procurement technique. [8, 9] Early work seems encouraging with centres across multiple different countries reporting positive outcomes [10 – 15]. Importantly there has yet to be a single reported post-operative death.

Here we aim to review mid-long term outcomes of international data from 59 *taNRP* cases from four centres – Royal Papworth Hospital UK, Vanderbilt University Medical Centre, USA, University Hospitals Leuven, Belgium, and Centre Hospitalier Universitaire, Liege Belgium since its introduction in February 2015.

Important to note the following definitions:
FWIT: time from a donor systolic pressure of 50mmHg to perfusion, with cold "cardioplegia" and a further cold ischaemic time making up a Total Ischemic Time (FTIT) which ends with reperfusion of the myocardium

Methods

Data was collected from four major transplant centres: Royal Papworth Hospital UK, Vanderbilt, USA, Centre Hospitalier Universitaire Liege, Belgium and University Hospitals Leuven, Belgium. Data was collected from pre-operative and intraoperative notes and collated in each centre before then being analysed as a whole. Analysis was performed using the Pandas Package on Python. The censor date was October 30, 2021. Continuous data with normal distribution are expressed with means and confidence intervals (*CI*), whereas continuous data with a non-normal distribution are presented with medians and interquartile ranges (*IQR*). Survival analysis was performed using Kaplan-Meier curves. Data comparison between the cold storage (CS) and ex-situ machine perfusion groups (ESMP) was performed, using the Wilcoxon rank sum test for continuous data and the Fisher test for categoric data. Statistical significance for the primary outcome was set at a 5% level. The technique utilised in the *taNRP* has been described in detail elsewhere.[10]

Results

The study covers an 84 month period which included a total of 132 years of cumulative survival after taNRP donor heart transplantation in 59 recipients. The outcomes of these 59 transplantations are shown below in Table 1. The median donor age was 29·5 years (*IQR = 21·5-37·5*), mean weight and height = 78·6kg (*65·75-91·35*) and 174·4cm (*169-180*) respectively. The average pre-withdrawal ejection fraction was 62% (n=47). Since the first taNRP in 2015 there have been no post-operative donor heart related deaths. There was only one intra-operative death in this series following acute aortic dissection at the time of cardiac implantation*. The median survival time was 430days and the mean survival was longer at 800 days. Post-transplant 30day survival (*n=59*), 1 year survival (*n=39*) and 5 year survival (*n=10*) were all 100%. However, all-cause mortality was 1·7%*. The mean functional ischaemic time (FTIT) was 16·8 minutes (n=53). The average ICU stay was 7.5 days (n=57) and mean ventilator time 30·3 hours (n=39). Nine patients required mechanical support in the early post-operative period (n=59). Of these, 8 required an intra-aorta balloon pump (*13·8%*), 1 required ECMO and 1 patient required both ECMO and an intra-aortic balloon pump (*3·4%*). Five patients required treatment for rejection (8·6% in n=58).

ESMP (ex-situ machine perfusion) vs CS (cold storage)

There was a significant difference in donor age, with donors whose hearts were preserved by ESMP (*Ex-Situ Machine Perfusion*) being significantly younger (39years vs 25years p = 0·00025). This is most likely due to the different hospitals which employed these preservation methods. The Royal Papworth Hospital in the UK used ESMP whereas centres in the US and Belgium both used CS. There was no significant difference in other donor characteristics between ESMP and CS, with mean height (175·2cm vs 174·4cm p=0·53), weight (81·9kg vs 78·6kg p=0·27) and ejection fraction (66% vs 61·3% p=0·34) being similar between ESMP and cold storage. There was no significant difference in the pre-operative pharmacological support with 50% vs 52·5% of patients on no support, 42% vs 40% of patients on one drug, 5·2% vs 5% of patients on two drugs and 0 vs 2·5% of patients on three drugs (p=1) for ESMP and CS respectively. The intra-operative parameters were largely similar with no significant difference found in the mean withdrawal to reperfusion time (24·8 vs 24·1 minutes p =0·22), mean withdrawal to the onset of functional total ischaemic time (FTIT) (9.1 vs 6.8 p=0.88) and FTIT to reperfusion (15·5 vs 17·3 p=0·62). There was no significant difference in MCS after transplantation. All-cause mortality was higher in the CS group due to intra-operative aortic dissection (0 vs 2·5%). But there was no difference in post-operative survival (100% vs 100%). However, there was a significant difference in mean ICU stay between the two groups (5 vs 7days p=0·046) and in donor age (39 vs 25years p=0·00026). Rates of acute rejection (15·7% vs 5·9% p=0·34) were not significantly different and nor was recipient age (55 vs 58years p=0·62)

Table 1. Outcomes in the 59 taNRP heart transplants:

Outcome	
Donor Characteristics	
Age, years, median (IQR) (n=59)	*29·5 (21·5-37·5)*
Height (mean +/- std) (n=59)	174·4 (169-180)
Weight (mean) (n=59)	78·6 (65·75-91·35)
Ejection Fraction (n=47)	62·0%
Pre-operative Pharmacological support	
No Pharmacological support (n=58)	30 (51·7%)
1 drug (n=58)	23 (39·7%)
2 drugs (n=58)	4 (6·9%)
3 drugs (n=58)	1 (1·7%)
Intraoperative Parameters	
Mean withdrawal to reperfusion time (std) (minutes in n=53)	24.2 (10·8)
Mean withdrawal to FTIT (std) (mins in n=53)	7.4 (6·3)
Mean FTIT to reperfusion (std) (mins in n=53)	16.8 (10·7)
Mechanical Circulatory Support (MCS) after transplantation (total number of patients, %) (n=58)	9 (15·5%)
IABP (n=58)	8 (13·8%)
ECMO (n=58)	2 (3·4%)
VAD (n=58)	0
Post-transplant outcomes	
All Cause mortality	1·7%
Post-transplant mortality	0%
30 Day survival (n=59) (IQR)	100%
1 year survival (n=39) (IQR)	100%
5 year survival (n=10) (IQR)	100%
Mean survival (days)	800
Median survival (days)	430
Cumulative survival after *taNRP* heart transplantation (years)	129
Ventilation, hours, median (IQR) (n=38)	12 (8·3-23·7)
ICU stay, days, median/ mean (IQR) n=(57)	7/ 7·53 (4-8)
Hospital stay, days, median/ mean (n=34)	17/ 20.3 (14·2-22·6)
Acute rejection 2R ACR (n=58)	5 (8·5%)
Recipient Age, years, median (IQR)	53·6 (45·5-62·5)

Table 2. Ex Situ Machine Perfusion (ESMP) vs Cold Storage during transportation:

Outcome	ESMP	Cold Storage	p-value
Donor Characteristics			
Age, years, median (IQR)	39 (14·5) (n=19)	25 (14·25) (n=40)	0·00025
Height (mean +/- std)	175·2 (10.4) (n=19)	174·4 (9·5) (n=40)	0·77
Weight (mean +/- std)	81·9 (19·4) (n=19)	78·6 (18·9) (n=40)	0·66
Ejection Fraction	66 (n=10)	61·3 (n =37)	0·21
Pre-operative Pharmacological support			
No Pharmacological support	9 (n=18)	21 (n=40)	1
1 drug	8 (n=18)	16 (n=40)	
2 drugs	1 (n=18)	2 (n=40)	
3 drugs	0 (n=18)	1 (n=40)	
Intraoperative Parameters			
Mean withdrawal to reperfusion time (minutes +/- std)	24·8 (12·5) (n=13)	24·1 (10·56) (n=40)	0·84
Mean withdrawal to onset of FTIT (minutes +/- std)	9·1 (6·0) (n=15)	6·8 (6·37) (n=40)	0·15
Mean FTIT to reperfusion (minutes +/- std)	15·5 (7·9) (n=13)	17·3 (11·58) (n=40)	0·62
Mechanical Circulatory Support (MCS) after transplantation (total number of patients, %)	5 (26) (n=19)	4 (10·2) (n=39)	1
IABP	5 (26) (n=19)	3 (7·7) (n=39)	
ECMO	1 (5·3) (n=19)	1 (2·6) (n=39)	
VAD	0	0	
Post-transplant outcomes			
All Cause mortality	0% (n=19)	2.5% (n=40)	
Post-transplant mortality	0% (n=19)	0% (n=39)	
30 Day survival	100% (n=19)	100% (n=39)	
1 year survival	100% (n=19)	100% (n=19)	
5 year survival	100% (n=10)	n/a	
Mean survival (days)	1786	364	n/a
Median survival (days)	1893	361	n/a
Ventilation, hours, median (IQR)	not available	12·5 (n=38)	n/a
ICU stay, days, median/ mean (IQR)	5/6·9 (n = 19)	7/7·8 (n=38)	0·046
Hospital stay, days, median/ mean	not available	17.0/20.3 (n=34)	
Acute rejection 2R ACR treated	3 (n=19: *15·8%*)	2 (n=34: *5·8%*)	0·34
Recipient Age, years, median (IQR)	55 (19) (n=19)	58 (15·25) (n=39)	0·43

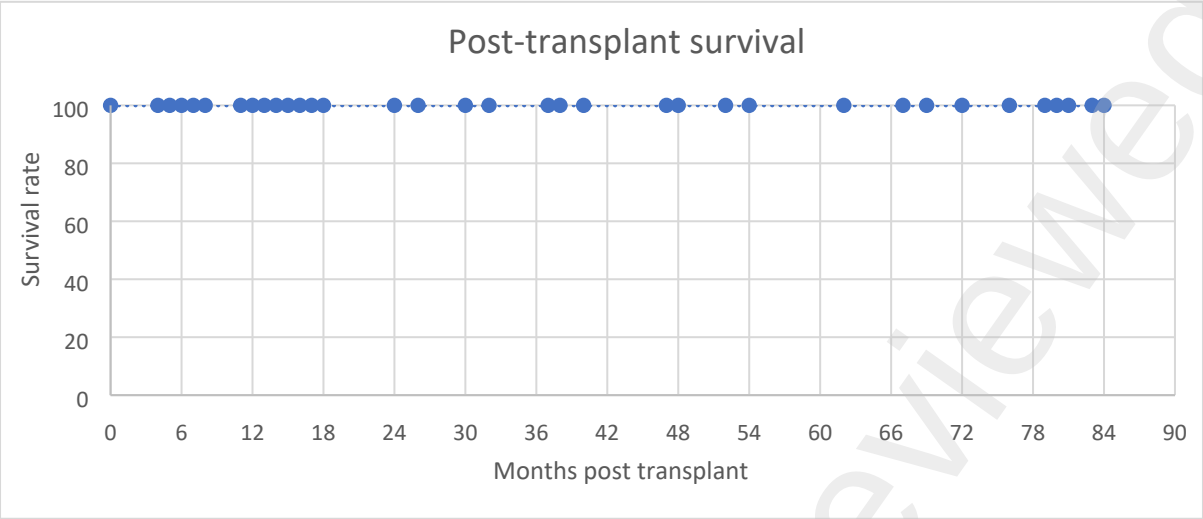

Figure 1 – Kaplan Meier Survival Curve of recipients post taNRP.

Table 3. Data points from Kaplan Meier Survival Curve

Number of patients alive	Time (months)	Survival (%)
58	0	100
58	4	100
53	5	100
49	6	100
45	7	100
44	8	100
41	11	100
38	12	100
37	13	100
33	14	100
31	15	100
27	16	100
24	17	100
23	18	100
22	24	100
21	26	100
20	30	100
19	32	100
18	37	100
16	38	100
15	40	100
14	47	100
13	48	100

12	52	100
11	54	100
10	62	100
9	67	100
8	69	100
7	72	100
6	76	100
5	79	100
4	80	100
3	81	100
2	83	100
1	84	100

Panel – Research in context

Systematic Review
We searched Pubmed with the terms 'taNRP', 'thoraco-abdominal normothermic regional perfusion', 'donation after circulatory death', 'donation after cardiac death', 'non heart beating donor' and 'heart transplantation'. DCD transplantation with direct procurement has shown its efficacy in the last few years. Outcomes of DCD transplantation with direct procurement are comparable to DBD transplantation. However, the outcomes from taNRP are extraordinarily. There have been 2 clinical case reports[11,12], as well as 4 countries detailing their early experiences of taNRP. [10, 13-15] All of these reports have been positive and there is yet to be a single reported death post taNRP.

Interpretation
To our knowledge, this is the first international case series reporting on long term (>=5 years) outcomes of taNRP. This study highlights the utility of taNRP in cardiac transplantation and the excellent outcomes associated with its use. Importantly there are no significant differences in survival between ESMP and CS, which may pave the way to a more effective, less expensive method of transplantation. taNRP has the potential to greatly reduce waiting lists and to significantly improve survival. It is of great importance therefore, that this technique becomes more widely utilised.

Discussion

This is the first international report on heart transplantation following *taNRP* utilizing both ESMP and CS. Remarkably, there have been no donor heart related deaths since its introduction in 2015 and there has been only one intraoperative death related to acute aortic dissection at the time of transplantation (*all-cause mortality of 1·7%*). Transplant heart related survival across the study period is 100%. This stands in contrast to direct procurement in both DCD and DBD heart transplantation patients, where there is a 10% mortality within the first year of life.[16] 7year survival after *taNRP* heart transplantation is 100% in this series.

The current results are dramatically better than previous reports of DCD heart transplant. The most plausible explanation, beyond the obvious small cohort and select high volume centres, is the short warm ischemic times in the series. *taNRP* aborts potentially longer ischemic times as compared to machine perfusion and even direct procurement. Tolerance to ischaemia before irreversible loss in cardiac tissue is about 30 minutes.[17] Therefore brevity of ischaemic time makes irreversible ischaemic cardiac damage less likely. Donors were also younger with a higher percentage of male donors. Both may be plausible reasons for the good postop outcomes. Whether there are any other advantages arising from in situ recovery of DCD heart function are not yet known.

It is also worth noting that there appears to be no significant difference in survival between hearts that were preserved by ESMP when compared to CS. In this way, *taNRP* may offer a more effective, cheaper method of heart transplantation. Although recipients who received hearts preserved by ESMP had a shorter ICU stay, it is not possible to say whether this was truly an added benefit of ESMP or due to some other reason. Clearly, more

work is needed to understand if ESMP has some short-term protective effect. However, in the mid-long term there seems to be no advantage offered by ESMP with regards to survival.

In the current series none of the CS or ESMP *taNRP* hearts were rejected for transplantation. Broader utilization of *taNRP* in DCD will undoubtedly have some hearts rejected, but this early experience is reassuring that the in situ assessment is sufficient to determine viability. Further work is necessary to develop novel biomarkers or consistent ways to assess the reanimated heart.

taNRP essentially enables the conversion of a DCD heart into a conventional donor, without the issue of the multiple effects of brain death on the potential donor heart.[18] Importantly, *taNRP* may increase the proportion of DCD hearts used for transplantation, minimise donor heart ischaemic times as well as improve outcomes for the recipient. This is very good news for of all those patiently awaiting a new heart on the lengthy waiting lists world-wide and paves the way to improved transplantation outcomes and shorter waiting times for donor hearts.

In conclusion, the is the first international, multicentre case series of *taNRP* resuscitated DCD hearts. Early results using a variety of techniques and assessment strategies are excellent. Future work will centre on optimizing this process and broadening the platform world-wide.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Data Sharing

Deidentified patient data may be made available by contacting the corresponding author after publication. Data will be shared with investigator support, after approval of a proposal. For data enquiries please contact jol20@cam.ac.uk

Author Contributions

Louca J – primary author – collected data, performed data analysis, wrote the paper.
Shah A – Initial acquisition of data, collected data and reviewed and commented on the paper.
Messer S– reviewed and commented on paper, contributed to initial conception of study.
Patel N – performed data analysis, reviewed and commented on the paper.
Sanghera R- performed data analysis, reviewed and commented on the paper.
Manara A – Reviewed and commented on the paper, initial design of study
Rubino A – Reviewed and commented on the paper, initial design of study
Rega F – Initial acquisition of data, collected data, reviewed and commented on the paper.
Tchana-Sato V – Initial acquisition of data, collected data, reviewed and commented on the paper.
Bhalla A – Performed data analysis and reviewed and commented on the paper.
Dubose Scarlett A – Initial acquisition of data, reviewed and commented on the paper
McMaster W – Initial acquisition of data, reviewed and commented on the paper
Berman M – Initial acquisition of data, reviewed and commented on the paper.
Large S – Reviewed and commented on the paper, Initial conception of the study.

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taNRP tables

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VAD (n=58)	0
Post-transplant outcomes	
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Table 2. Ex Situ Machine Perfusion (ESMP) vs Cold Storage during transportation:

Outcome	ESMP	Cold Storage	p-value
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Intraoperative Parameters			

Mean withdrawal to reperfusion time (minutes +/- std)	24·8 (12·5) (n=13)	24·1 (10·56) (n=40)	0·84
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Mechanical Circulatory Support (MCS) after transplantation (total number of patients, %)	5 (26) (n=19)	4 (10·2) (n=39)	1
IABP	5 (26) (n=19)	3 (7·7) (n=39)	
ECMO	1 (5·3) (n=19)	1 (2·6) (n=39)	
VAD	0	0	
Post-transplant outcomes			
All Cause mortality	0% (n=19)	2.5% (n=40)	
Post-transplant mortality	0% (n=19)	0% (n=39)	
30 Day survival	100% (n=19)	100% (n=39)	
1 year survival	100% (n=19)	100% (n=19)	
5 year survival	100% (n=10)	n/a	
Mean survival (days)	1786	364	n/a
Median survival (days)	1893	361	n/a
Ventilation, hours, median (IQR)	not available	12·5 (n=38)	n/a
ICU stay, days, median/ mean (IQR)	5/6·9 n = 19	7/7·8 (n=38)	0·046
Hospital stay, days, median/ mean	not available	17.0/20.3 (n=34)	
Acute rejection 2R ACR treated	3 (n=19: *15·8%*)	2 (n=34: *5·8%*)	0·34
Recipient Age, years, median (IQR)	55 (19) (n=19)	58 (15·25) (n=39)	0·43

Table 3. Data points from Kaplan Meier Survival Curve

Number of patients alive	Time (months)	Survival (%)
58	0	100
58	4	100
53	5	100
49	6	100
45	7	100
44	8	100
41	11	100
38	12	100
37	13	100
33	14	100
31	15	100

27	16	100
24	17	100
23	18	100
22	24	100
21	26	100
20	30	100
19	32	100
18	37	100
16	38	100
15	40	100
14	47	100
13	48	100
12	52	100
11	54	100
10	62	100
9	67	100
8	69	100
7	72	100
6	76	100
5	79	100
4	80	100
3	81	100
2	83	100
1	84	100

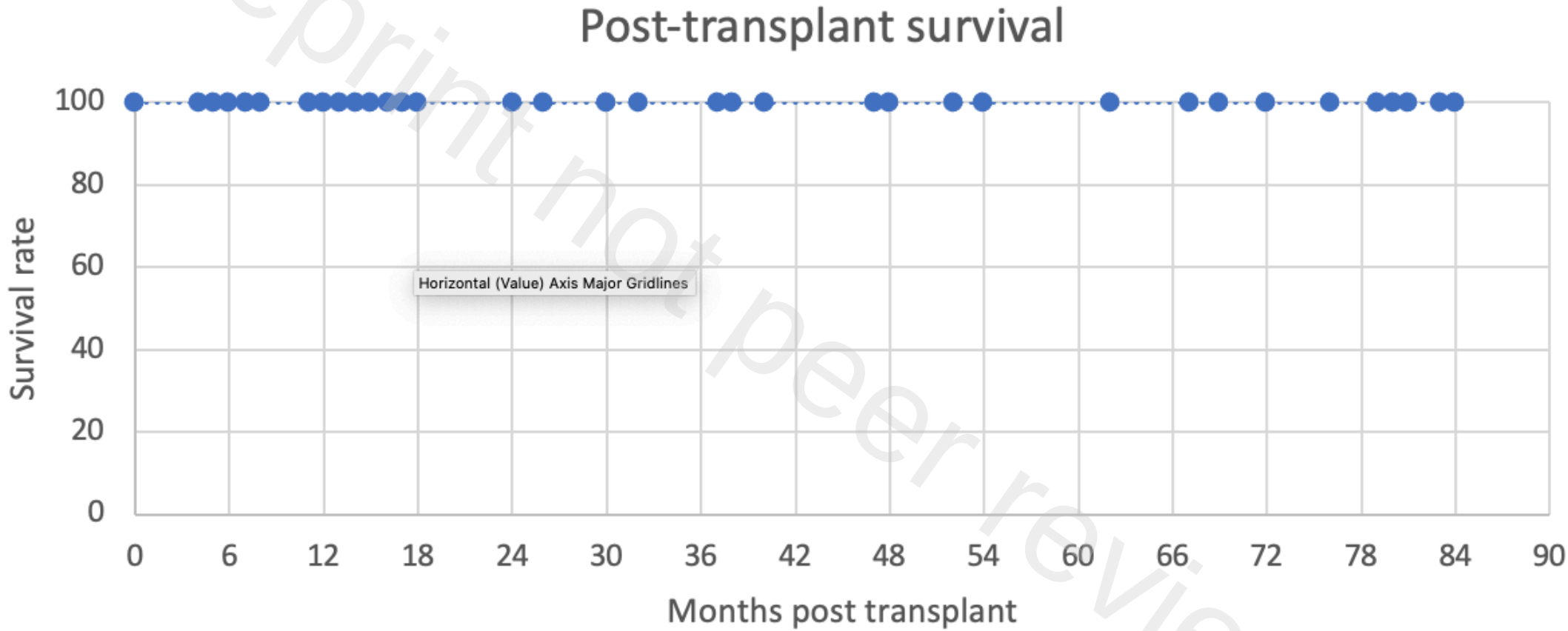

Figure 1 – Kaplan Meier Survival Curve of recipients post taNRP.