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ORIGINAL ARTICLE

Comparing short-term/long-term outcomes of heart transplants that occur inside and outside of normal working hours

Hidefumi Nishida[1]*, Christopher Salerno[1], David Onsager[1], Tae Song[1], Ann Nguyen[2], Jonathan Grinstein[2], Bow Chung[2], Bryan Smith[2], Sara Kalantari[2], Nitasha Sarswat[2], Gene Kim[2], Sean Pinney[2], Valluvan Jeevanandam[1] and Takeyoshi Ota[1]

[1]*Department of Surgery, The University of Chicago Medicine, Chicago, IL, USA; and* [2]*Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA*

Abstract

Aims Heart transplantation involves many factors such as donor selection, recipient management, multidisciplinary assessment, coordination with other organ teams, and transportation. Because of some unpredictable factors, heart transplantation can be conducted at any time of day. The purpose of this study is to investigate if outcomes differ between heart transplants taking place inside or outside of normal working hours.

Methods and results We reviewed patients who underwent heart transplantation at our institution from January 2010 to July 2020 (n = 329). Based on the documented start time of the recipient surgeries, the cohort was divided into two groups: working hours (Group A: 7:30 to 17:00; n = 92) and after hours (Group B: 17:00 to 7:30; n = 237). We compared these groups using propensity score matching analysis. After propensity score matching, 78 pairs of patients were successfully matched. We reviewed early and late clinical outcomes including survival. Long-term survival was compared using the Kaplan–Meier method. In the propensity-score matched patients, there were no significant differences in the baseline characteristics between two groups. In-hospital mortality was not significantly different between the two groups (Group A: 6.4% vs. Group B: 2.6%, P = 0.44). Ischaemic time and cross-clamp time did not differ between the groups. In terms of postoperative complications, there were no significant differences between two groups in stroke (6.4% vs. 3.9%, P = 0.72), primary graft dysfunction requiring extracorporeal membrane oxygenation (5.1% vs. 7.7%, P = 0.75), re-exploration for bleeding (9.0% vs. 12.8%, P = 0.44), and newly required haemodialysis (7.7% vs. 6.4%, P = 0.75). The survival rate in Group A (88.1% at 1 year, 81.3% at 3 years) was not significantly different from Group B (90.5% at 1 year, 82.3% at 3 years, log rank = 0.96).

Conclusion There was no significant difference in clinical outcomes between heart transplants taking place inside or outside of working hours. A high quality of care can be provided for heart transplant patients even during after hours.

Keywords Heart; Transplantation; Working hours; Outcome; Circadian rhythm

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**Correspondence to: Hidefumi Nishida, Department of Surgery, Section of Cardiac Surgery, The University of Chicago, 5841S Maryland Avenue, MC5040, Chicago, Illinois 60637, USA. Phone: 773-702-2500; Fax: 773-834-9114. Email: hnishida@bsd.uchicago.edu*

Introduction

The clinical outcomes of heart transplantation have improved over the decades.[1] A number of predictors of mortality in heart transplantation have been identified including advanced age, reoperation, requiring mechanical circulatory support, and newly occurred tricuspid regurgitation.[2–4] Heart transplantation involves many factors such as donor selection, recipient management, multidisciplinary assessment, coordination with other organ teams, and transportation. However, it remains unknown if the fact that the heart transplantation is performed in the middle of the night would affect on clinical outcomes. Because it is unpredictable when donors become available, heart transplantations could be conducted at any time of the day. In some reports, clinical outcomes vary depending on the time of the day a surgery takes place.[5–7] The purpose of this study is to investigate if clinical outcomes differ between heart transplants taking place inside or outside of normal working hours.

Methods

Patients and study design

The cohort included consecutive patients undergoing heart transplantation at our institution from January 2010 to July 2020 (n = 329). Based on the documented start time of surgery, the cohort was divided into two groups: working hours (Group A: 7:30 to 17:00; n = 92) and after hours (Group B: 17:00 to 7:30; n = 237), and compared perioperative data and late outcomes including long-term survival using the Kaplan–Meier method. A propensity score matching analysis was also performed. After propensity score matching, 78 pairs of patients were successfully matched. The mean follow-up period was 43.0 ± 32.7 months after transplantation. The definition of ischaemic time is from cross clamp of the donor aorta to removing cross clamp of the recipient aorta. Our standard regimen of postoperative protocol and immunosuppressive therapy is as follows. Immunosuppressive therapy included steroids, calcineurin inhibitor, and mycophenolate mofetil. Steroids were tapered to off over 10–12 months. Therapeutic drug monitoring of calcineurin inhibitor was performed periodically. Serum immunoglobulin levels were measured at 1 week, 4 weeks, 3 months, and 1 year following heart transplantation. Additional measurements could be made at physician discretion. Endomyocardial biopsy was performed routinely throughout the first 2 years post-transplant in accordance with our standard protocol, and additionally, when rejection was suspected.

The institutional review board of our institution approved this study and the requirement for informed consent was waived.

Statistical analyses

All data analyses were performed with JMP 11.0 software (SAS Institute Inc, Cary, NC, USA). Data were expressed as means ± standard deviations or median and ranges for continuous variables and as numbers (percentages) for categorical variables. Comparisons of continuous variables were tested with unpaired t-test or Mann–Whitney U-test depending on normal distribution or not. Comparisons of categorical variables were tested with χ^2 test or Fisher's exact test; χ^2 test was used for categorical variables when the data value for each cell was five or higher. Otherwise, we used Fisher's exact test. Late survival was analysed using the Kaplan–Meier method and a log-rank test.

The propensity scores were obtained using a multivariate logistics regression model with transplant started in working hours as the dependent variable. In the multivariate model, the following 21 baseline characteristics were used as covariates: donor age, donor body mass index, recipient age, gender, aetiology of heart failure, body mass index, previous cardiac surgery, hypertension, dyslipidaemia, diabetes mellitus, history of atrial fibrillation, history of cerebral vascular accident, chronic obstructive pulmonary disease, peripheral vascular disease, creatinine, blood urea nitrogen, haemoglobin, platelet, intra-aortic balloon pump (IABP) support, ischaemic time, and preoperative central venous pressure. The matching model achieved a good discriminatory power (C-statistics 0.702). Matching was performed using a 1:1 nearest-available matching algorithm without replacement, with a ±0.2 calliper width. For all comparisons, $P < 0.05$ was considered significant.

Results

Baseline characteristics

Baseline patient characteristics are presented in *Table 1*. In the unmatched overall cohort, the patients in Group A (51.2 ± 14.7 years old) was significantly younger than patients in Group B (54.6 ± 12.4 years old) (P = 0.03). There were not any significant differences in gender, hypertension, diabetes mellitus, creatinine, and ejection fraction. Half or more patients had history of previous cardiac surgery (A: 46/92; 50.0% vs. B: 125/237; 52.7%, P = 0.66). Fifty patients (54.4%) in Group A and 104 patients (43.9%) in Group B were on IABP support before the heart transplantation (P = 0.09). There were no significant differences in the haemodynamics parameters between two groups. In the propensity-matched cohort (78 pairs), there were no significant differences in baseline characteristics including haemodynamic data between two groups.

Operative data

Time distribution of the cases is shown in *Figure 1*. Operative data are detailed in *Table 2*. In the unmatched overall cohort, the bicaval anastomosis technique was utilized in 61 patients (65.9%) in Group A and 169 patients (71.1%) in Group B, respectively (P = 0.37). There was also no significant difference in the anastomosis techniques in the matched cohort.

In the matched cohort, the donor heart ischaemic time (A: 239.3 ± 61.0 min vs. B: 242.1 ± 65.2 min, P = 0.78), cardiopulmonary bypass time (201.2 ± 58.7 vs. 199.6 ± 64.9, P = 0.87), cross clamp time (151.2 ± 38.7 vs. 149.0 ± 42.1, P = 0.73), and implant time (90.4 ± 21.7 vs. 87.3 ± 21.3, P = 0.38) did not

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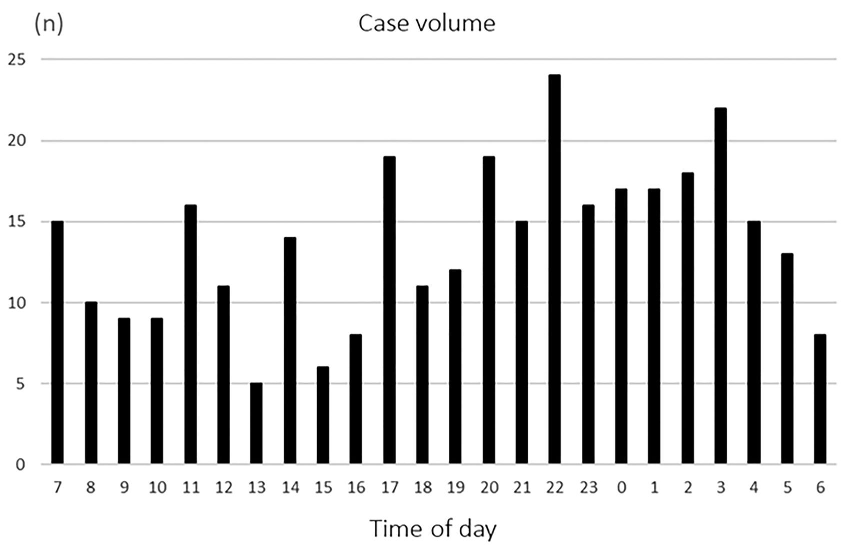
Table 1 Baseline preoperative characteristics

	Unmatched patients			Propensity-matched patients		
	Group A (*n* = 92)	Group B (*n* = 237)	*P*	Group A (*n* = 78)	Group B (*n* = 78)	*P*
Donor age (years old)	31.7 ± 9.9	32.8 ± 10.8	0.38	32.8 ± 10.9	32.2 ± 10.0	0.75
Donor gender male	58 (63.7%)	144 (62.1%)	0.78	49 (62.8%)	49 (62.8%)	1.00
Donor body mass index (kg/m^2)	28.0 ± 7.0	27.2 ± 6.8	0.33	28.1 ± 7.1	27.5 ± 6.1	0.53
Mean age (years old)	51.2 ± 14.7	54.6 ± 12.4	0.03	51.8 ± 14.5	51.5 ± 13.2	0.89
Male	70 (76.1%)	188 (79.3%)	0.52	61 (78.2%)	58 (74.4%)	0.57
Body mass index (kg/m^2)	29.0 ± 12.6	27.9 ± 5.0	0.49	28.6 ± 4.8	28.3 ± 5.4	0.71
Hypertension	51 (55.4%)	136 (57.4%)	0.75	44 (56.4%)	42 (53.9%)	0.75
Dyslipidaemia	33 (36.3%)	92 (38.8%)	0.67	27 (34.6%)	25 (32.1%)	0.73
Diabetes mellitus	28 (30.4%)	73 (30.8%)	0.95	23 (29.5%)	23 (29.5%)	1.00
Cerebrovascular accident	9 (9.8%)	17 (7.2%)	0.44	8 (10.3%)	6 (7.7%)	0.57
History of atrial fibrillation	36 (39.1%)	99 (41.8%)	0.66	32 (41.0%)	34 (43.6%)	0.75
COPD	4 (4.4%)	13 (5.5%)	0.67	4 (5.13%)	7 (8.97%)	0.53
Peripheral vascular disease	1 (1.1%)	10 (4.2%)	0.12	1 (1.28%)	1 (1.28%)	1.00
Non-ischaemic cardiomyopathy	65 (70.7%)	153 (64.6%)	0.44	53 (68.0%)	50 (64.1%)	0.61
Previous cardiac surgery	46 (50.0%)	125 (52.7%)	0.66	42 (53.9%)	38 (48.7%)	0.52
Intra-aortic balloon pump	50 (54.4%)	104 (43.9%)	0.09	42 (53.9%)	38 (48.7%)	0.52
ECMO	1 (1.1%)	5 (2.1%)	0.51	1 (1.3%)	1 (1.3%)	1.00
Creatinin (mg/dL)	1.41 ± 0.9	1.44 ± 1.0	0.78	1.44 ± 0.9	1.38 ± 0.7	0.65
BUN (mg/dL)	27.8 ± 16.7	25.0 ± 16.0	0.17	27.1 ± 15.1	26.3 ± 16.7	0.77
Haemoglobin (g/dL)	11.2 ± 1.9	11.3 ± 2.1	0.74	11.2 ± 1.9	10.9 ± 2.0	0.27
Platelet (10*3/μL)	21.0 ± 7.6	20.1 ± 7.8	0.36	20.8 ± 7.6	21.8 ± 8.4	0.44
LV diastolic diameter (mm)	66.8 ± 11.3	66.2 ± 13.1	0.67	66.7 ± 11.3	64.6 ± 12.4	0.29
Ejection fraction (%)	23.5 ± 11.1	24.4 ± 10.7	0.53	23.3 ± 11.1	24.7 ± 10.8	0.42
Central venous pressure (mmHg)	11.3 ± 7.0	9.7 ± 6.3	0.06	11.1 ± 6.8	12.5 ± 6.5	0.21
Mean PAP (mmHg)	31.2 ± 10.9	28.7 ± 10.4	0.07	31.7 ± 11.0	32.5 ± 10.9	0.67
PAWP (mmHg)	20.6 ± 9.2	18.9 ± 8.8	0.16	21.1 ± 9.0	22.1 ± 9.1	0.51
Cardiac index (L/min/m^2)	2.36 ± 0.7	2.38 ± 0.6	0.85	2.34 ± 0.7	2.35 ± 0.7	0.93

COPD, chronic obstructive pulmonary disorder; ECMO, extracorporeal membranous oxygenation; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure.

Figure 1 Distribution of case volume.



differ between two groups. There were five surgeons who performed heart transplants. Out of 329 transplants, 233 (70.8%) were performed by surgeon #1, 67 (20.4%) by surgeon #2, 15 (4.6%) by surgeon #3, 7 (2.1%) were performed by surgeon #4, and 7 (2.1%) were performed by surgeon #5.

We also investigated if the operation room team members of the transplants performed in after hours have started their work in working hours. From March 2013 to July 2020, 180 heart transplants were performed in after hours. Out of 180 cases, surgeons have started their work in working hours in

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81 cases (45%), anaesthesiologists in 125 cases (69.4%), perfusionists in 112 cases (62.2%), and nurses in 120 cases (66.7%).

Early clinical outcomes

Early clinical outcomes are shown in *Table 3*. Overall, there were 17 in-hospital mortality (17/329, 5.2%). The cause of in-hospital mortality included heart failure in nine patients (2.7%), respiratory failure in three patients (0.9%), stroke in two patients (0.6%), septic shock in one patient (0.3%), subarachnoid haemorrhage in one patient (0.3%), and acute pancreatitis in one patient (0.3%). No significant difference was noted between two groups in in-hospital mortality both in the unmatched cohort (6.5% vs. 4.6%, P = 0.50) and in the matched cohort (6.4% vs. 2.6%, P = 0.44). In the matched cohort, there were no significant differences in the postoperative complications including re-exploration for bleeding (9.0% vs. 12.8%, P = 0.44), extracorporeal membranous oxygenation (ECMO) requirement (5.1% vs. 7.7%, P = 0.75), haemodialysis (7.7% vs. 6.4%, P = 0.75), and stroke (6.4% vs. 3.9%, P = 0.72).

Late survival

Overall, the survival rate in Group A (87.6% at 1 year, 80.1% at 3 years, and 77.6% at 5 years) was not significantly different from Group B (90.9% at 1 year, 84.6% at 3 years and 79.9% at 5 years, log rank = 0.75) (*Figure 2*). In matched cohort, the survival rate in Group A (88.1% at 1 year, 81.3% at 3 years, 81.3% at 5 years) was not also significantly different from Group B (90.5% at 1 year, 82.3% at 3 years, 77.5% at 5 years, log rank = 0.96) (*Figure 3*).

Discussion

It has been unknown if the time of the day when a surgery takes place has an impact on clinical outcomes.[5–8] In particular, it would be an important factor because heart transplantation could occur at any time of the day due to the nature of the process of organ donations. This study demonstrated that the clinical outcomes, including in-hospital mortality, postoperative complications, and late survival of heart transplantation, were consistent regardless of the inside or outside of working hours.

Outcomes of cardiac/transplant surgery taking place inside or outside of working hours

In cardiac surgery, many medical personnel resources are required in the operating room and in the intensive care unit postoperatively. However, it is a chronic issue to be understaffed during outside of working hours in many institutions.[9]

Table 2 Operative data

	Unmatched patients			Propensity-matched patients		
Variables	Group A (n = 92)	Group B (n = 237)	P	Group A (n = 78)	Group B (n = 78)	P
Operative procedures						
Bicaval anastomosis	61 (65.9%)	169 (71.1%)	0.37	52 (66.7%)	55 (70.5%)	0.61
Ischaemic time (min)	237.0 ± 60.2	230.9 ± 58.9	0.42	239.3 ± 61.0	242.1 ± 65.2	0.78
Cardiopulmonary bypass time (min)	198.5 ± 57.5	196.2 ± 57.4	0.75	201.2 ± 58.7	199.6 ± 64.9	0.87
Cross clamp time (min)	149.4 ± 37.3	146.7 ± 37.1	0.57	151.2 ± 38.7	149.0 ± 42.1	0.73
Implant time (min)	89.2 ± 21.2	87.1 ± 18.8	0.40	90.4 ± 21.7	87.3 ± 21.3	0.38

Table 3 Early clinical outcomes

	Unmatched patients			Propensity-matched patients		
Variables	Group A (n = 92)	Group B (n = 237)	P	Group A (n = 78)	Group B (n = 78)	P
In-hospital mortality	6 (6.5%)	11 (4.6%)	0.50	5 (6.41%)	2 (2.56%)	0.44
Re-exploration for bleeding	8 (8.7%)	24 (10.2%)	0.68	7 (8.97%)	10 (12.8%)	0.44
ECMO	5 (5.4%)	21 (8.9%)	0.28	4 (5.13%)	6 (7.69%)	0.75
Haemodialysis	8 (8.7%)	15 (6.4%)	0.46	6 (7.69%)	5 (6.41%)	0.75
Stroke	6 (6.5%)	7 (3.0%)	0.16	5 (6.41%)	3 (3.85%)	0.72
Central venous pressure (mmHg)	8.2 ± 4.8	7.8 ± 4.2	0.43	8.3 ± 4.5	8.9 ± 4.7	0.41
Mean PAP (mmHg)	23.9 ± 6.2	24.1 ± 7.2	0.78	23.7 ± 6.1	26.1 ± 8.9	0.06
PCWP (mmHg)	15.2 ± 5.4	15.1 ± 5.6	0.95	14.9 ± 5.3	16.7 ± 6.5	0.08
Cardiac index (L/min/m^2)	3.04 ± 0.7	3.04 ± 0.6	0.96	3.05 ± 0.8	3.03 ± 0.6	0.87

ECMO, extracorporeal membranous oxygenation; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure.

Figure 2 Freedom rates from all cause death of Group A and Group B in unmatched cohort. Kaplan–Meier survival estimates and log rank test has shown no difference between two groups.

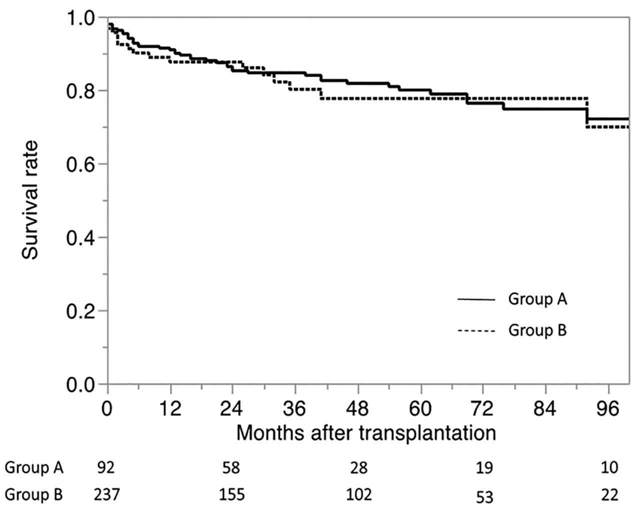
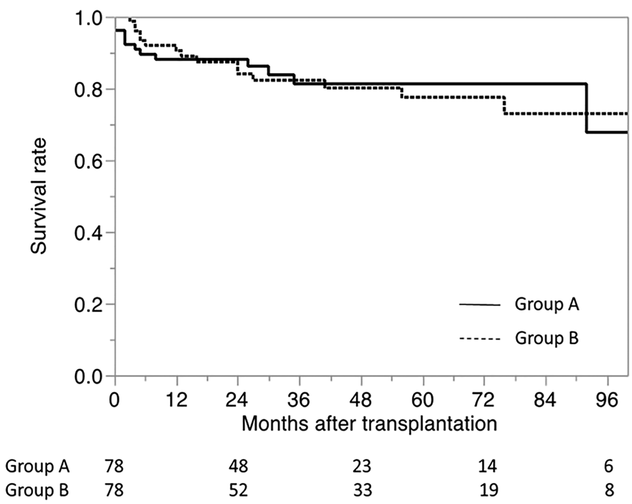


Figure 3 Freedom rates from all cause death of Group A and Group B in matched cohort. Kaplan–Meier survival estimates and log rank test has shown no difference between two groups.



It is reasonable to assume that it could negatively affect the outcomes in cardiac surgery where a decent number of surgery conducted during outside of working hours. Yount and colleagues reported that mortality and cost were significantly higher in patients who underwent surgery after 3 p.m. compared with before 3 p.m. in a 3395 non-emergent cardiac case review.[10] On the other hand, Heller and colleagues reported the mortality and major complications in elective cardiac surgery started during night time (between 4 p.m. and 6 a.m.) was not significantly different compared with those started during day time.[6] Even though these studies investigated only elective cardiac surgery cases, the outcome is not consistent. The next question is: when it comes to emergent cardiac surgeries that could happen any time of the day, would inside versus outside working hours impact clinical outcomes?

Working in after hours would cause disturbance of circadian rhythm of team members in operation room including surgeons, anaesthesiologists, nurses, and perfusionists. Although it is well known that the disturbance of circadian rhythm can adversely affect such as subjective alertness, cognitive performance, haemodynamics (i.e. heart rate and blood pressure), hormone secretion (i.e. cortisol), and immune system, little is known about how this disturbance affect clinical performance of team members.[11–13] Our study demonstrated that the clinical outcomes including in-hospital mortality, postoperative complications, and late survival of heart transplantation were consistent regardless of the inside or outside of working hours. Because little is known about the impact of surgery timing on clinical outcomes of heart transplantation, our outcomes could not be compared with others. There are some reports regarding outcomes of liver or kidney transplantation during outside of the working hours. Becker and colleagues analysed their 350 orthotopic liver transplantation data (154 during day time and 196 during night time), which showed no significant differences in early mortality, surgical complications, and 1 year survival.[14] In contrast, Lonze and colleagues investigated their 578 liver transplantation experience, which showed higher mortality within 7 days after transplant performed at night.[15] Kienzl-Wagner and colleagues reported, in 873 kidney transplants, there was no correlation between mortality, surgical complication, and 5 year outcomes between night time (n = 263) and day time (n = 610) procedures.[16] On the other hand, Fechner and colleagues reported night time kidney transplantation was associated with higher complications and graft failure.[17] The mixed findings imply that transplant surgery involves multiple factors affecting clinical outcomes. We believe that these findings would be applicable to heart transplantation as well. However, because we could not demonstrate how the disturbance of circadian rhythm affected subjective alertness, cognitive performance, haemodynamics, and hormone secretion of operation room team members scientifically, further study would be warranted.

Team experience and case volume

In addition to inside/outside of the working hours, team experience and the case volume would be important confounding factors to affect clinical outcomes in emergent cardiac cases. In emergent cardiac surgery such as type A dissection or heart transplantation, not only the time of the day but also the surgeons' experience and hospital case volume are reportedly associated with clinical outcomes.[18–20] Dobaria and colleagues investigated 25 231 patients received type A aortic dissection repair from database of the National Inpatient Sample in the USA and reported that the mortality in low-volume hospitals (21.5%) was significantly higher than that in high-volume hospitals (11.6%, $P < 0.01$).[19] As for heart transplantation, Arnaoutakis and colleagues demonstrated that low case volume was associated with worse mortality.[21] In an effort to improve clinical outcomes in cardiac surgery, it has been proposed to establish an experienced surgical team consists of surgeons, anaesthesiologists, nurses, and other medical staff.[22,23] Andersen and colleagues reported that their multidisciplinary surgical programme including such as surgeons, physicians, blood bank, nursing, and perfusion specialists improved operative mortality significantly.[22] In our institution, the multidisciplinary care team involved experienced surgeons, anaesthesiologists, mid-level providers, nursing staffs, perfusion specialists, pre-operative, and post-operative transplant coordinators, pharmacists, and social workers in the management of heart transplantation. In order to investigate the impact of experience of surgeons, we divided our surgeons into two groups (surgeon #1 vs. surgeon #2, #3, #4, #5) and analysed outcomes. But there were no significant differences between two groups in early outcomes and late survival. Although we are not able to demonstrate the scientific data how each member contributes to clinical outcomes, each specialist works efficiently and cooperatively in each field to maintain high quality as a team even during outside of working hours. An established multidisciplinary team covering inside and outside working hours would be an important key to improve clinical outcomes.

There are some limitations to be addressed. First, this is a retrospective and single-centre study. A prospective randomized study would be ideal to determine the impact of the time of operation for the outcomes of heart transplantation, which would not be feasible due to the nature of transplant surgery. Therefore, we performed a propensity matching analysis to improve the reliability of the study. Second, the definition of working hours and after hours might be different in each hospital. We divided 24 h into the working hours (7:30–17:00) and after hours (17:00–7:30) in accordance with the policy in our hospital. Third, we could not include data about the duration of the underlying disease and time spent on heart failure and medication due to lack of data. Fourth, further follow up would be warranted to clarify the impact of the time of operation in heart transplantation.

Conclusion

There was no significant difference in clinical outcomes between heart transplants taking place inside or outside of working hours. A high quality of care can be provided to heart transplant patients both in inside and outside of the working hours with a great team effort.

Conflict of interest

None declared.

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