Cold ischemia >4 hours increases heart transplantation mortality. An analysis of the Spanish heart transplantation registry

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Abstract

Background: Cold ischemia time (CIT) has been associated to heart transplantation (HT) prognosis. However, there is still uncertainty regarding the CIT cutoff value that might have relevant clinical implications.

Methods: We analyzed all adults that received a first HT during the period 2008–2018. CITwas defined as the time between the cross-clamp of the donor aorta and the reperfusion of the heart. Primary outcome was 1-month mortality.

Results: We included 2629 patients, mean agewas 53.3±12.1 years and 655 (24.9%) were female. Mean CIT was 202 ± 67 min (minimum 20 min, maximum 600 min). One-month mortality per CIT quartile was 9, 12, 13, and 19%. One-year mortality per CIT quartile was 16, 19, 21, and 28%. CIT was an independent predictor of 1-month mortality, but only in the last quartile of CIT >246 min (odds ratio 2.1, 95% confidence interval 1.49–3.08, $p < .001$). We found no relevant differences in CIT during the study period. However, the impact of CIT in 1-month and 1-year mortality decreased with time (p value for the distribution of ischemic time by year 0.01), particularly during the last 5 years.

Conclusions: Although the impact of CIT in HT prognosis seems to be decreasing in the last years, CIT in the last quartile (> 246 min) is associated with 1-month and 1-year mortality. Our findings suggest the need to limit HT with CIT N> 246 min or to use different myocardial preservation systems if the expected CIT is> 4 h.

1. Introduction

Heart transplantation (HT) is the treatment of choice for carefully selected patients with advanced or end-stage heart failure [1], with a median survival around 12 years. Among the different factors that may influence the prognosis of HT [2], cold ischemia time (CIT) has been associated with primary graft failure and mortality [3] and is one of the most important risk factors for early graft dysfunction [4]. However, there is still uncertainty regarding the CIT cutoff value that might have relevant clinical implications. The recent changes in HT have included an increase in donors and recipients age, in the rate of emergent transplantation, and, according to some data, of CIT [5]. Yet, this change has not been associated with higher mortality [6]. Although different strategies have been developed in order to expand the pool of donors, including donation-after-circulatory-death and TransMedics® Organ Care System [7] the vast majority of HT are done with hearts preserved in cold systems [8].

The aim of our study was to examine, in a large National consecutive HT registry, the trend of CIT in the last decade, as well as its influence on 30-day and 1-year.

2. Methods

2.1. Population and data collection

Our data come from the Spanish Heart Transplantation Registry, a prospective database promoted by the Working Group in Heart Failure of the Spanish Society of Cardiology that contains detailed clinical information about all HT performed in our nation. The registry is updated in a yearly basis with data supplied by all HT centers of the country. This database has been described elsewhere [6]. For the purpose of this study, data regarding CIT, baseline recipient characteristics, donor, surgical procedure, and survival were obtained from the database.

2.2. Study population

This was a retrospective analysis involving recipients from 17 participating centers who fulfilled the following inclusion criteria: 1) Recipient of a first isolated HT between January 2008 and November 2018; 2) Age at transplant >16 years; 3) Information of CIT available. CIT was defined as the time between the cross-clamp of the donor aorta and the reperfusion of the heart. The Spanish system tries to minimize the distance between donor and recipient but also prioritizes emergencies. First level emergencies have National priority.

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committees of all the participating centers.

2.3. Statistical analysis

Data are presented as median with interquartile range (IQR) for continuous variables and frequency with percentage for categorical variables. Comparison between groups was conducted by use of Mann-Whitney U analysis. Categorical variables were compared by using $\chi2$ or Fisher exact tests. Association between variables was assessed by using linear regression analysis and correlation by means of the non-parametric Spearman rho. CIT quartiles were used to assess the influence of CIT in prognosis. The primary outcome was 1-month mortality. One-year survival was also analyzed as secondary outcome. Univariate relations between variables and the primary endpoint were assessed by logistic regression analysis. Multiple logistic regression model was built using stepwise backward model after excluding those with >10% of missing data. Multiple logistic was repeated including those variables with imputation of missing data without relevant changes (data not shown). The logrank test was used to compare survival among the 4 CIT quartiles. Statistical analysis was performed using the Stata 13.0 package (StataCorp LP, Tx).

3. Results

A total of 2977 HT were included in the registry during the study period but 348 were excluded from this study (232 age < 16 years, 57 combined transplantation, 46 retransplantation, and 13 CIT unavailable). The final population of 2629 had a mean age of 53.3 ± 12.1 years and 655 women (24.9%). Mean CIT was 202 ± 67 min (minimum 20 min, maximum 600 min). Table 1 shows characteristics according to CIT quartile (Table 1). Urgent HT, mechanical ventilation and ventricular assist device were more common in the upper CIT quartiles.

Table 1. Baseline characteristics according to cold ischemia time (CIT) quartile.

Characteristic	Ischemic time quartiles				p-value
	≤ 159 min	160–210 min	211–246 min	> 246 min	
	Mean ± SD or no. (%) (n = 664)	Mean ± SD or no. (%) (n = 724)	Mean ± SD or no. (%) (n = 591)	Mean ± SD or no. (%) (n = 650)	
A) Recipients					
Age. mean ± SD	53.8 ± 11.8	53.7 ± 11.2	52.8 ± 12.3	52.6 ± 12.4	0.326
Sex (males)	503 (75.8)	552(76.2)	425(71.9)	494(76.0)	0.632
BMI. mean ± SD	25.5 ± 3.91	25.5 ± 4.13	25.4 ± 3.92	25.8 ± 4.18	0.224
Cardiomyopathy					
Nonischemic dilated cardiomyopathy	268(40.4)	280(38.7)	234(39.6)	226(34.8)	0.558
Ischemic dilated cardiomyopathy	181(27.3)	214(29.6)	168(28.4)	226(34.8)	
Valvular	39(5.9)	36(5.0)	41(6.9)	44(6.8)	
Others	176(26.5)	194(26.8)	148(25.0)	154(23.7)	
PVR (UW). mean ± SD	2.2 ± 1.2	2.3 ± 1.5	2.3 ± 1.7	2.1 ± 1.3	0.130
Creatinine >2 mg/dl	30(4.5)	39(5.4)	23(3.9)	36(5.6)	0.667
Bilirubin >2 mg/dl	116(18.9)	109(16.4)	89(16.4)	103(17.6)	0.541
Diabetes mellitus	135(20.5)	149(20.7)	126(21.4)	146(22.7)	0.308
COPD moderate-severe	68(11.2)	81(12.0)	59(10.4)	57(8.9)	0.130
Previous infection	69(10.4)	93(12.9)	93(15.7)	124(19.2)	<0.001
Previous thoracic surgery	142(21.5)	187(25.9)	181(31.0)	226(34.9)	<0.001
Urgent transplant	186(28.0)	271(37.4)	287(48.6)	311(47.9)	<0.001
Mechanical ventilation prior to transplant	63(9.6)	77(10.7)	107(18.1)	138(21.5)	<0.001
VAD prior to HT					
No	490(74.4)	480(67.0)	337(57.2)	368(57.0)	<0.001
IABP	62(9.4)	89(12.4)	89(15.1)	89(14.7)	
ECMO	47(7.1)	52(7.3)	61(10.4)	67(10.4)	
Continuous flow-VAD	47(7.1)	79(11.0)	74(12.6)	82(12.7)	
Pulsatile flow-VAD	13(2.0)	16(2.2)	28(4.8)	34(5.3)	
B) Donor					
Age. mean ± SD	43.8 ± 12.5	43.2 ± 12.5	43.4 ± 12.6	42.1 ± 12.7	0.085
Sex (males)	408(61.54)	447(61.7)	369(62.5)	440(67.7)	0.023
Female donor/male recipient	163(24.6)	169(23.3)	117(19.8)	125(19.2)	0.007
Weight. mean ± SD	77.1 ± 14.4	76.3 ± 13.8	76.4 ± 13.3	77.1 ± 14.3	0.581
Weight recipient/donor >1.20	57(8.7)	72(10.0)	41(7.0)	71(10.9)	0.453
Weight recipient/donor <0.8	123(18.7)	118(16.3)	106(18.0)	112(17.2)	0.683
Cause of death					
Cerebrovascular	395(59.6)	405(56.1)	336(57.1)	366(56.8)	0.265

B) Donor					
Traumatism	167(25.2)	205(28.4)	150(25.5)	165(25.6)	
Others	101(15.2)	112(15.5)	103(17.5)	113(17.6)	

C) Complications and mortality					
Primary graft failure	125(19.2)	159(22.3)	128(22.5)	184(29.5)	<0.001
ICU stay length	9.7 ± 11.5	10.6 ± 13	12.4 ± 15.1	11.9 ± 16.2	<0.001
CAV	56(8.4)	74(10.2)	48(8.1)	49(7.5)	0.337
Infection	231(38.8)	259(39.4)	206(40.5)	189(33.9)	0.148
Hypertension	232(40.0)	278(44.7)	200(39.7)	238(43.8)	0.495
Diabetes					
No	370(66.5)	411(66.4)	332(66.7)	357(66.9)	0.769
Diet	10(1.8)	14(2.3)	17(3.4)	15(2.8)	
Oral antidiabetics	47(8.3)	56(9.1)	45(9.0)	40(7.5)	
Insulin	134(23.5)	138(22.3)	104(20.9)	122(22.9)	
Neurologic disease	60(10.4)	91(14.6)	87(17.4)	104(19.2)	<0.001
Renal replacement therapy	38(6.7)	50(8.1)	42(8.4)	56(10.4)	0.030
Permanent pacemaker	31(5.6)	31(5.2)	22(4.6)	15(2.9)	0.034
1-month mortality	58(8.7)	86(11.9)	74(12.5)	121(18.6)	<0.001
1-year mortality	104(15.7)	140(19.3)	125(21.2)	179(27.5)	<0.001

BMI: body mass index. PVR: pulmonary vascular resistance. COPD: chronic obstructive pulmonary disease. VAD: ventricular assistance device. IABP: Intraaortic balloon pump. ECMO: extracorporeal membrane oxygenation.
ICU: Intensive care unit. CAV: Cardiac Allograft Vasculopathy.

The rate of primary graft failure increased with CIT quartile, and was particularly high in the last quartile (19% - 22% - 23% - 30%). This was also the case with 1-month (9% - 12% - 13% - 19%) and 1-year (16% - 19% - 21% - 28%) mortality. Table 2 shows univariate and multivariate logistic regression analysis for 1-month and 1-year mortality (Table 2). CIT was an independent predictor of 1-month mortality (odds ratio [OR] per min 1.00, 95% confidence interval [CI] 1.00–1.01, p < .001). CIT was also an independent predictor of 1-year mortality (OR per min 1.00, 95% CI 1.00–1.01, p < .001). Of note, in both cases, the independent influence of CIT in the prognosis was only seen in the last quartile. shows the Kaplan-Meier curves according to CIT quartile.

Table 2. Univariate and multivariate logistic regression analysis for A) 1-month mortality and B) 1-year mortality

	OR (95% CI)	p-value	% missing
A			
Ischemic time	1.00 (1.00–1.01)	<0.01	0.49
Recipient data			
Age	1.00 (0.99–1.01)	0.565	0.00
Sex (Female)	1.18 (0.92–1.52)	0.197	0.00
BMI	1.00 (0.98–1.03)	0.750	0.11
Cardiomyopathy			
Nonischemic dilated cardiomyopathy			
Ischemic dilated cardiomyopathy	1.12 (0.85–1.49)	0.423	0.00
Valvular	1.49 (0.94–2.35)	0.087	
Others	1.22 (0.92–1.63)	0.172	
Kidney failure	1.44 (1.12–1.86)	<0.01	3.10
Creatinine	1.12 (0.97–1.31)	0.133	0.45
Bilirubin >2 mg/dl	1.74 (1.31–2.30)	<0.01	8.52
PVR	1.08 (1.00–1.17)	0.046	16.24
Previous infection	1.81 (1.36–2.40)	<0.01	0.23
Diabetes Mellitus	0.97 (0.73–1.28)	0.824	0.64
COPD moderate-severe	1.10 (0.76–1.60)	0.598	5.19
Mechanical ventilation	2.50 (1.91–3.27)	<0.01	0.79
VAD prior to HT	1.38 (1.10–1.74)	<0.01	0.72
Previous thoracic surgery	1.41 (1.11–1.80)	<0.01	0.64
Emergency level (emergent/elective)	0.70 (0.56–0.88)	<0.01	0.00
Donor data			
Age	1.01 (1.00–1.02)	0.175	0.08
Sex (Female)	1.00 (0.79–1.26)	0.967	0.08
Cause of death			
Cerebrovascular			
Traumatism	1.03 (0.79–1.34)	0.813	0.45
Others	0.85 80.61–1.18)	0.332	

	Multivariate OR (95% CI)	p-value
1-month mortality		
Cold ischemia time		
1 - ≤159 min	1	
2–160-210 min	1.37 (0.94–1.99)	0.11
3–211-246 min	1.33 (0.90–1.98)	0.15
4 - >246 min	2.14 (1.49–3.08)	<0.01

	Multivariate OR (95% CI)	p-value	
1-month mortality			
Transplant year	0.94 (0.90–0.98)	<0.01	
Kidney failure	1.42 (1.07–1.88)	0.01	
Bilirubin ≥2 mg/dl	1.55 (1.15–2.08)	<0.01	
Mechanical ventilation	2.24 (1.67–3.01)	<0.01	
Previous thoracic surgery	1.37 (1.05–1.78)	0.02	

	OR (95% CI)	p-value	% missing
B			
Ischemic time	1.00 (1.00–1.01)	<0.01	0.49
Recipient data			
Age	1.01 (1.00–1.02)	<0.01	0.00
Sex (Female)	1.17 (0.95–1.45)	0.142	0.00
BMI	1.02 (0.99–1.04)	0.129	0.11
Cardiomyopathy			
Nonischemic dilated cardiomyopathy			
Ischemic dilated cardiomyopathy	1.08 (0.86–1.36)	0.524	0.00
Valvular	1.27 (0.86–1.88)	0.227	
Others	1.12 (0.88–1.43)	0.345	
Kidney failure	1.62 (1.31–2.00)	<0.01	3.10
Creatinine	1.32 (1.12–1.55)	<0.01	0.45
Bilirubin >2 mg/dl	1.69 (1.33–2.14)	<0.01	8.52
PVR	1.05 (0.98–1.13)	0.155	16.24
Previous infection	1.82 (1.43–2.32)	<0.01	0.23
Diabetes Mellitus	1.10 (0.88–1.38)	0.406	0.64
COPD moderate-severe	1.15 (0.85–1.55)	0.374	5.19
Mechanical ventilation	2.39 (1.89–3.02)	<0.01	0.79
VAD prior to HT	1.50 (1.24–1.82)	<0.01	0.72
Previous thoracic surgery	1.31 (1.07–1.61)	<0.01	0.64
Emergency level (emergent/elective)	0.65 (0.65–0.78)	<0.01	0.00
Donor data			
Age	1.00 (1.00–1.01)	0.220	0.08
Sex (Female)	0.97 (0.80–1.18)	0.764	0.08
Cause of death			
1-Cerebrovascular			
2-Traumatism	1.01 (0.81–1.26)	0.937	0.45
3- Others	0.83 (0.63–1.09)	0.186	

	Multivariate OR (95% CI)	p-value
1-year mortality		
Cold ischemia time		
1 - ≤159 min	1	
2–160-210 min	1.25 (0.93–1.67)	0.14
3–211-246 min	1.29 (0.94–1.76)	0.11
4 - >246 min	1.83 (1.36–2.45)	<0.01
Transplant year	0.95 (0.92–0.98)	<0.01
Recipient age	1.01 (1.00–1.02)	0.02
Kidney failure	1.57 (1.25–1.98)	<0.01
Bilirubin ≥2 mg/dl	1.55 (1.20–2.00)	<0.01
Mechanical ventilation	2.21 (1.71–2.86)	<0.01
Previous thoracic surgery	1.31 (1.05–1.64)	0.02

Kidney failure: creatinine >2 mg/dl. PVR: Pulmonary Vascular Resistance. VAD: Ventricular assist device (includes ECMO). OR: odds ratio. CI: confidence interval.

We found no relevant differences in CIT during the study period (Fig. 2). However, the impact of CIT in 1-month and 1-year mortality decreased with time (p value for Kruskal-Wallis test to the distribution of ischemic time by year 0.01) (Supplementary Figure), particularly during the last 5 years.
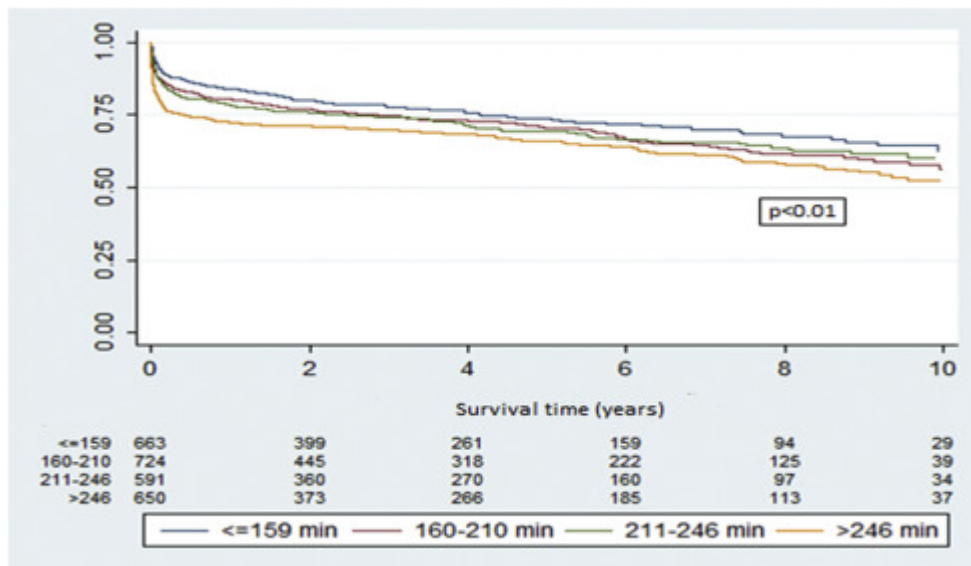

Fig. 1. Kaplan-Meier curves according to cold ischemia time quartile, *p* value for the log-rank test.
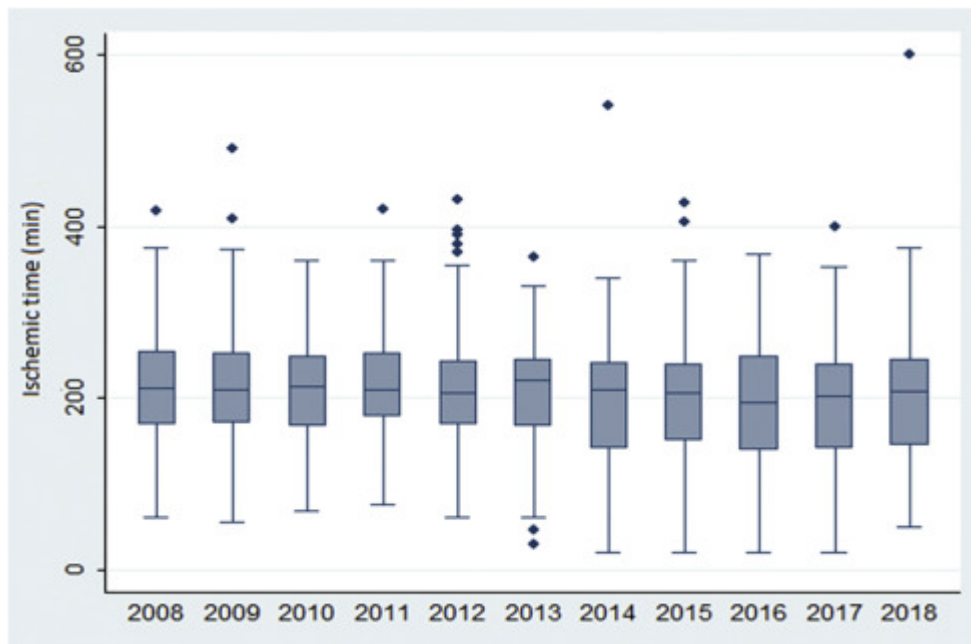
Fig. 2. Cold ischemia time during each year of the study period.

4. Discussion

Our main finding is that, although the impact of CIT in HT prognosis seems to be decreasing in the last years, CIT in the last quartile (>246 min) is associated with 1-month and 1-year mortality.

The association of CIT with HT prognosis has been previously described [[9], [10], [11], [12]]. However, there still is uncertainty regarding the prognostic effect of CIT and of the cutoff value that might have relevant clinical implications. Some studies have reported no differences in survival even with prolonged CIT [13,14] or have described different cutoffs [15,16].

Our data suggest that we should be concern when ischemic time is longer than 4 h. Del Rizzo et al. also found a clear relation of CIT >4 h with mortality, but only in donors >50 years [17]. Their small sample size (only 372) might have been underpowered to detect the prognostic influence with younger donors. In fact, even in children, CIT >3.5 h implies an increased risk of graft loss [18]. Reich et al. studied the influence of donor age in CIT prognostic effect [12], under the hypothesis that older donors could be more susceptible to prolonged CIT but found no significant differences. We were also unable to find a specific effect of donor age in CIT prognostic effect.

Two previous single-center studies were unable to find an influence of CIT in the prognosis of HT [13,14]. The first was focused on long-term survival [13] and compared 4 CIT groups (<150, 150–200, 200–250, >250 min), of note only 80 had CIT >250 min and this low number probably limited the power to detect CIT prognostic influence. In fact, the only independent predictor the authors were able to find was recipient female sex. The second study [14] compared 46 HT with CIT >300 min with 46 case-matched controls. Although 30-day mortality in patients with CIT > 300 min was twice that in controls, both groups had a very low 30-day mortality [4.3% vs. 2.1%], compared with our 12.9%. In fact, in that study, only 3 patients died in the 30-day period. One of the strengths of our study is the large number of patients in the upper quartile [650]. Moreover,

previous thoracic surgery, that in our study was an independent predictor of mortality, is also associated to longer CIT [19].
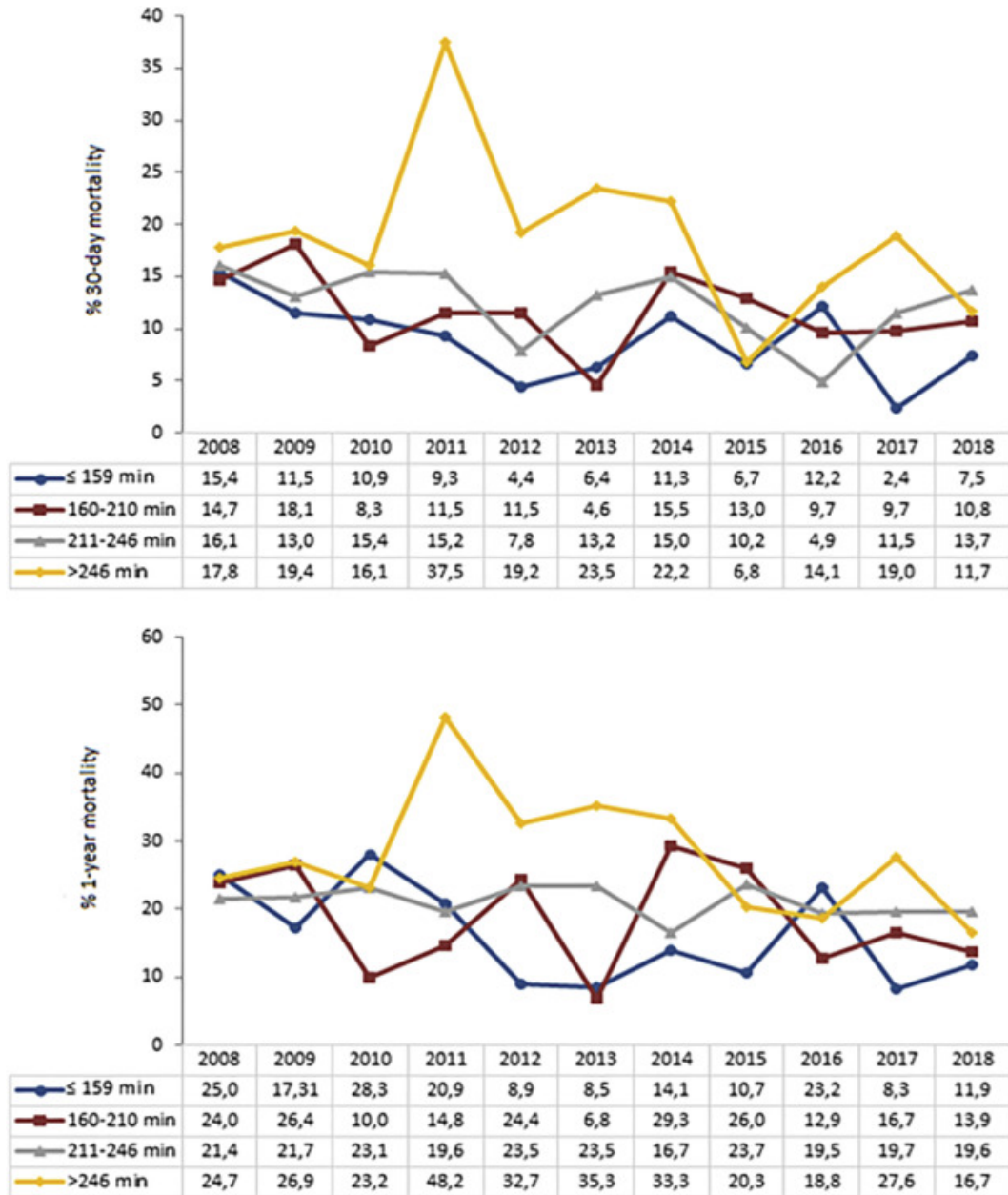
Although some authors have described an increase in CIT during a 10-year period [20], our data do not support this increase. However, the peculiarities of the Spanish National Transplant System [21] might protect our centers from such increase. In any case, our data suggest that the influence of CIT in prognosis is decreasing, as can be seen in the yellow lines depicted in the Supplementary Figure. The reasons why the effect of prolonged CIT might be reduced in the most recent era are unknown. The increasing use of mechanical circulatory support might make recipients in better overall condition at the time of transplant. Also, the better selection of donors, including, when possible, avoiding sex mismatch in male recipients [22,23] might play a role.

Patients in the lower CIT quartile were supported by a ventricular assist device less often than patients in the upper quartile. However, in our registry, ventricular assist device prior to HT was not a risk factor for mortality at 1-month or 1-year after HT, a finding previously described [24,25]. In any case, it is clear that patients with prolonged CIT had a greater risk profile. In fact, compared to recipients with shorter CIT, they had more frequently variables that might be associated with a poor prognosis. These variables include not only circulatory support but also prior infection, previous thoracic surgery, urgent transplant, and mechanical ventilation. All these variables were included in the multivariable analysis. However, it is conceivable that multivariate analysis was not able to correct completely all the differences regarding the risk profile of the four CIT quartiles.

Our study has more limitations. Missing data could have influenced our results. Although in most variables the rate of missing values was extremely low, in some of then, as pulmonary vascular resistance, was higher than 10%. The data came from Spain, with specific patient characteristics and, even more so, logistics, criteria for distribution, and distance from donor to recipient centers. So, the extrapolation of our findings to other health systems should be done with caution. In any case the homogeneity of our National transplant system is also an advantage as decreases the possibility of bias. For instance, in Spain HT after TransMedics ® Organ Care System or donation-after-circulatory-death have not been performed.

In conclusion, although the impact of CIT in HT prognosis seems to be decreasing in the last years, CIT in the last quartile (>246 min) is associated with 1-month and 1-year mortality. Our findings suggest the need to limit HT with CIT > 246 min or to use different myocardial preservation systems if the expected CIT is >4 h.

The following is the supplementary data related to this article

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
≤ 159 min	15,4	11,5	10,9	9,3	4,4	6,4	11,3	6,7	12,2	2,4	7,5
160-210 min	14,7	18,1	8,3	11,5	11,5	4,6	15,5	13,0	9,7	9,7	10,8
211-246 min	16,1	13,0	15,4	15,2	7,8	13,2	15,0	10,2	4,9	11,5	13,7
>246 min	17,8	19,4	16,1	37,5	19,2	23,5	22,2	6,8	14,1	19,0	11,7

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
≤ 159 min	25,0	17,31	28,3	20,9	8,9	8,5	14,1	10,7	23,2	8,3	11,9
160-210 min	24,0	26,4	10,0	14,8	24,4	6,8	29,3	26,0	12,9	16,7	13,9
211-246 min	21,4	21,7	23,1	19,6	23,5	23,5	16,7	23,7	19,5	19,7	19,6
>246 min	24,7	26,9	23,2	48,2	32,7	35,3	33,3	20,3	18,8	27,6	16,7

Supplementary Figure 1. Thirty-day and 1-year mortality according to cold ischemia time quartile during each year of the study period.

Authorship contributions

Conception and design of study: MMS.
Acquisition of data: All.
Analysis and/or interpretation of data: MJVM, MMS.
Drafting the manuscript: MJVM, MMS.
Revising the manuscript critically for important intellectual content: All.
Approval of the version of the manuscript to be: All.

Declaration of Competing Interest

None.

References

[1]   M.G. Crespo-leiro, M. Metra, L.H. Lund, et al. Advanced heart failure: a position statement of the heart failure Association of the European Society of cardiology. Eur. J. Heart Fail., 20 (2018), pp. 1505-1535

[2]   K.K. Khush, W.S. Cherikh, D.C. Chambers, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-fifth adult heart transplantation report - 2018; focus theme: multiorgan transplantation. J. Hear Lung Transpl., 37 (2018), pp. 1155-1168

[3]   J.Segovia, M.D.G. Cosío, J.M. Barceló, et al. RADIAL: a novel primary graft failure risk score in heart transplantation. J. Hear Lung Transpl., 30 (2011), pp. 644-651

[4]   S.S.A. Singh, J.R. Dalzell, C. Berry, N. Al-Attar Primary graft dysfunction after heart transplantation: a thorn amongst the roses. Heart Fail. Rev., 24 (2019 Sep), pp. 805-820

[5]   I. Kim, J. Youn, I. Kim The past, present and future of heart transplantation. Korean Circ. J., 48 (2018), pp. 565-590

[6]   F. González-Vílchez, M. Gómez-Bueno, L. Almenar-Bonet, et al. 28th official report of the spanish society of cardiology. Working Group on Heart Failure (1984–2016). Rev. Esp. Cardiol. (Engl Ed), 70 (2017), pp. 1098-1109

[7]   A. Ardehali, F. Esmailian, M. Deng, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet., 385 (2015), pp. 2577-2584

[8]   M.M. Vela, D.G. Sáez, A.R. Simon Current approaches in retrieval and heart preservation. Ann. Cardiothorac. Surg., 7 (2018), pp. 67-74

[9]   Chambers DC, Yusen RD, Cherikh WS, et al. The registry of the international society for heart and lung transplantation: thirty-fourth adult lung and heart-lung transplantation report — 2017; focus theme: allograft ischemic time. J. Hear Lung Transplant. 2017;36:1047–59.

[10]   Rossano JW, Cherikh WS, Chambers DC, et al. The registry of the international society for heart and lung transplantation: twentieth pediatric heart transplantation report — 2017; focus theme: allograft ischemic time. J. Hear Lung Transplant. 2017;36:1060–69.

[11]   A. Nicoara, D. Ruffin, M. Cooter, et al. Primary graft dysfunction after heart transplantation: Incidence, trends, and associated risk factors. Am. J. Transpl., 18 (2018), pp. 1461-1470

[12]   H.J. Reich, J.A. Kobashigawa, T. Aintablian, D. Ramzy, M.M. Kittleson, F. Esmailian. Effects of older donor age and cold ischemic time. Tex. Heart Inst. J., 45 (2018), pp. 17-22

[13]   J.A. Morgan, R. John, A.D. Weinberg, et al. Prolonged donor ischemic time does not adversely affect long-term survival in adult patients undergoing cardiac transplantation. J. Thorac. Cardiovasc. Surg., 126 (2003), pp. 1624-1633

[14] F.A. Mitropoulos, J. Odim, D. Marelli, et al. Outcome of hearts with cold ischemic time greater than 300 minutes. A case-matched study. Eur. J. Cardiothorac. Surg., 28 (2005), pp. 143-148

[15] M.E Currie, Y. Shudo, Y.J. Woo. Successful outcome following orthotopic heart transplantation with a donor half way across the country. Transplant. Proc., 50 (2018), pp. 4062-4063

[16] R.A. Sorabella, L. Guglielmetti, A. Kantor, et al. Cardiac donor risk factors predictive of short-term heart transplant recipient mortality: an analysis of the united network for organ sharing database. Transplant. Proc., 47 (2015), pp. 2944-2951

[17] D.F. Del Rizzo, A.H. Menkis, P.W. Pflugfelder, et al. The role of donor age and ischemic time on survival following Orthotopic heart transplantation. J. Hear Lung Transpl., 2498 (1999), pp. 310-319

[18] M.A. Ford, C.S. Almond, K. Gauvreau, et al. Association of Graft Ischemic Time with survival after heart transplant among children in the United States. J. Hear Lung Transpl., 30 (2011), pp. 1244-1249

[19] T. Aziz, M. Burgess, A. Rahman, C. Campbell, A. Deiraniya, N. Yonan. Early and long-term results of heart transplantation after previous cardiac surgery. Eur. J. Cardiothorac. Surg., 17 (2000), pp. 349-354

[20] N.R. Banner, H.L. Thomas, E. Curnow, J.C. Hussey, C.A. Rogers. The importance of cold and warm cardiac ischemia for survival after heart transplantation. Transplantation., 86 (2008), pp. 542-547

[21] Distribution Criteria of Heart Transplantation, National Transplant Organization (2019) http://www.ont.es/infesp/CriterioDeDistribucion/Criterios%20distribuci%C3%B3n%20C oraz%C3%B3n%202019.pdf

[22] A. Ayesta, G. Urrútia, E. Madrid, et al. Sex-mismatch influence on survival after heart transplantation: a systematic review and meta-analysis of observational studies. Clin. Transpl., 33 (2019), Article e13737, 10.1111/ctr.13737

[23] M. Martinez-Selles, L. Almenar, M.J. Paniagua-Martin, et al. Donor/recipient sex mismatch and survival after heart transplantation: only an issue in male recipients? An analysis of the Spanish heart transplantation registry. Transpl. Int., 28 (2015), pp. 305-313

[24] F. Kamdar, R. John, P. Eckman, M. Colvin-Adams, S.J. Shumway, K. Liao. Postcardiac transplant survival in the current era in patients receiving continuous-flow left ventricular assist devices. J. Thorac. Cardiovasc. Surg., 145 (2013), pp. 575-581

[25] The International Society for Heart and Lung Transplantation International Thoracic Organ Transplant Registry Data https://ishltregistries.org/registries/slides.asp (2019)