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Clinical outcome and quality of life of patients surviving 20 years or longer after heart transplantation

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Summary

To evaluate outcome and quality of life (QoL) in ≥20 years survivors after heart transplantation. Patients surviving ≥20 years with a single graft were retrospectively reviewed. Heterotopic, multiorgan and retransplantations were excluded. QoL was evaluated using the SF-36 survey. Eight hundred and twenty-seven heart transplants were performed from 1981 to 1993, and among these, 131 (16%) patients survived ≥20 years; 98 (75%) were male and mean age at transplant was 43 ± 13 years. Conditional survival in these 20 years survivors was 74.1 ± 4.3% at 23 years and 60.9 ± 5.3% at 25 years (45 deaths, 34%). Forty-four (34%) patients suffered rejection ≥2R. Conditional survival free from rejection ≥2R was 68 ± 4.1% at 5 years and 66.4 ± 4.2% at 10 years. Thirty-five (27%) patients had cardiac allograft vasculopathy (CAV) grade 2–3. Conditional CAV-free survival was 76 ± 3.8% at 20 years and 72.1 ± 4% at 25. Sixty-nine (53%) patients developed malignancy, mostly skin cancers. Conditional malignancy-free survival was 53.5 ± 4.4% at 20 years and 45.2 ± 4.6% at 25 years. At latest follow-up, 24.0 ± 3.0 years after transplantation, mean left ventricular ejection fraction was 62 ± 11% and mean physical and mental scores were 57 ± 23 and 58 ± 21, respectively. Sixteen per cent of heart recipients survived ≥20 years with good ventricular performance and QoL. CAV and malignancies account for late morbidity and mortality.

Introduction

Cardiac transplantation represents the treatment of choice for selected patients with end-stage heart failure [1]. Since the introduction of cyclosporine in the early 1980s, major advances have been made, both in diagnosis and treatment of graft dysfunction, rejection and infection leading to significant improvement in graft and recipient survival [2–5]. In addition to improved survival, heart transplantation has also been shown to significantly improve recipient's quality of life (QoL), at least for 5 years after transplantation [6]. However, late complications such as cardiac allograft vasculopathy (CAV) and adverse effects related to prolonged immunosuppression still continue to limit long-term survival and might also affect QoL. Only a limited number of studies have focused on heart transplant recipients surviving more than 20 years after transplantation. Furthermore, previous studies have mainly concentrated on long-term survival and transplant-related complications such as CAV, rejection, malignancies and infection [7]. Therefore, the aim of the present retrospective single-centre study was to evaluate, in addition to morbi-mortality, QoL in a large cohort of patients surviving 20 years or longer after heart transplantation.

Patients and methods

Study population

Medical records of all OHT recipients surviving more than 20 years with a single graft were reviewed retrospectively.

Patients undergoing heterotopic heart transplantation, multiorgan transplantation and retransplantation were excluded from the study. Data were collected until September 2013.

Operative technique

Grafts were harvested from beating-heart brain-dead donors, preserved using cold crystalloid heart preservation solutions and stored in cold saline solution during transportation. OHT was performed according to the bi-atrial technique developed by Lower and Shumway [8].

Immunosuppression

All patients received immunosuppressive treatment consisting of antilymphocyte globulin (Thymoglobulin®; Genzyme Transplant, Cambridge, MA, USA) at a dose of 1.5 mg/kg/day for the first 5 postoperative days and preoperative intravenous methylprednisolone and azathioprine. Postoperatively patients received cyclosporine 4–6 mg/kg/day (target level 300 ng/ml), azathioprine 25–50 mg/day and prednisone 1 mg/kg/day which was progressively reduced to 0.2 mg/kg/day. Minimization of immunosuppression by lower levels of CNI (adapted for serum level of 50–100 ng/ml) and corticosteroids (5–10 mg/day) was common practice and safe in this population. Patients' regimens were modified during follow-up visits and switched to tacrolimus, mycophenolate mofetil, sirolimus or everolimus as appropriate (acute rejection, CAV, malignancies). High-dose corticosteroid was the first line therapy for acute cellular rejection with grade more than 1R.

Follow-up

Patients have been followed closely and received routine laboratory tests, clinical examination, echocardiography, endomyocardial biopsy (EMB) and coronary angiography according to our institution protocols. Patients were monitored by repetitive EMBs to detect rejection; EMBs were performed approximately 15–20 times during the first year post-transplant, three times during the second year and twice a year from the third to the tenth year. After 10 years, echocardiography and cardiac examination were performed twice a year, and EMB was performed only in case of clinical suspicion of rejection. Coronary angiography was performed once every 2 year; in presence of CAV, coronary angiography was performed every year and in case of coronary angioplasty and stenting, a control angiography was performed 6 months after the procedure. Total body dermatological examination and total body computed tomography were performed once every 2 years for skin and solid cancer screening, respectively. Upper gastrointestinal endoscopy and colonoscopy were performed in the presence of anaemia or symptoms. The following post-transplant events were recorded for all patients: rejection grade ≥2R and CAV grades 2 and 3, defined according to ISHLT classifications [9,10]. Furthermore, all malignancies (including lymphoid, nonlymphoid and skin malignancies) and all infections requiring hospitalization for IV antibiotics administration were noted.

Quality-of-life assessment

Quality-of-life assessment of more than 20 years survivors was performed using the French version of the short-form (SF)-36 health survey [11]. The SF-36 survey was sent by mail or administered in eligible consenting patients during their last follow-up by one of the authors (A.G.). Contemporary heart transplant recipients surviving more than 1 year but <20 years were used as controls.

The SF-36 is a generic health survey designed to assess aspects of health that are not disease, treatment, or age specific. The SF-36 is a generic multidimensional instrument consisting of eight multi-item components representing physical functioning (PF; the extent to which health limits physical activities, such as self-care, walking, climbing stairs), role functioning physical (RP; the extent to which physical health interferes with work or other daily activities); bodily pain (BP; the intensity of pain and the effect of pain on normal work, both inside and outside the home); general health perceptions (GH; personal evaluations of current health, health outlook, and resistance to illness); vitality (VT; feeling full of energy rather than tired and worn out); social functioning (SF; the extent to which physical health or emotional problems interfere with normal social activities); role functioning emotional (RE; the extent to which emotional problems interfere with work or daily activities); and mental health (MH; general mental health including depression, anxiety, behavioural-emotional control, and general positive affect). These eight scales can be aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores. SF-36 scores are expressed on a scale that runs from 0 to 100, a higher score indicating a better quality of life.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 statistical software (SPSS Inc, Chicago, IL, USA). Categorical variables were expressed as percentages and continuous variables were expressed as the mean ± 1 SD and compared using the Student's *t*-test. Survival data were analysed with standard Kaplan–Meier techniques for estimation of survival probabilities and compared using the log-rank test. A

two-tailed P value of <0.05 was taken to indicate statistical significance.

Results

From January 1981 to September 1993, a total of 827 OHTs were performed at our institution in 813 patients, including 14 retransplantations. Three hundred thirteen (38%) patients died during the first year post-transplant, 349 (43%) died during postoperative years 1–19, and 20 (2%) were lost to follow-up. The remaining 131 (16%) patients survived for more than 20 years with a single graft and are the main focus of this study. Characteristics of recipients and donors at the time of transplantation are illustrated in Table 1. Indication for transplantation included dilated cardiomyopathy in 75 (57%) patients, ischaemic cardiomyopathy in 32 (24%), valvular cardiomyopathy in 10 (8%), hypertrophic cardiomyopathy in 9 (7%), and other causes in 5 (4%).

Survival

Forty-five (34%) of the 131 patients who had survived more than 20 years died at a mean of 22.7 ± 2.0 years (range: 20.1–27.4) after transplant and at a mean age of 66.4 ± 11.0 years (range: 43.1–87.3). Survival estimates conditional to 20 years survival were 74.1 ± 4.3% at 23 years, 60.9 ± 5.3% at 25 years and 46.8 ± 6.2% at 27 years (Fig. 1). Estimation of mean survival was 27.2 ± 0.5 years (95% confidence interval, 26.2–28.2 years) with a median survival of 26.5 ± 0.8 years. There was no significant difference in survival (P = 0.12) between patients transplanted during the first part (from 1981 to 1988) and the second part (from 1989 to 1993) of the study period. The main causes of death were related to CAV (n = 15, 33%), graft failure (n = 13, 29%), septic shock (n = 12, 27%), and malignancy (n = 4, 9%; 3 lymphoma and 1 nonlymphoid malignancy) and pulmonary embolism (n = 1, 2%).

Table 1. Characteristics of recipients and donors at time of transplantation; data are expressed as mean ± SD and frequencies (percentages).

Variable	Recipients (n = 131)	Donors (n = 131)
Age (years)	42.9 ± 12.8 (10.7–67.8)	31.5 ± 12.3 (9–59)
Sex M/F (%M)	98/33 (75%)	103/23 (78%)
Sex mismatch	25 (19%)	
Height (cm)	169.3 ± 8.6 (133–192)	172.5 ± 10.0 (120–190)
Weight (Kg)	64.2 ± 12.5 (21–92)	69.1 ± 11.2 (30–90)
BMI (m^2)	22.3 ± 3.2 (11.8–30.1)	23.1 ± 2.6 (16–33)
HLA matching	62 (47%)	
1 locus	38 (29%)	
2 loci	18 (14%)	
3 loci	5 (4%)	
4 loci	1 (1%)	
Graft ischaemic time (min)	123 ± 56 (29–360)	

BSA, body surface area; HLA, human leucocyte antigen.

Rejection

Allograft rejection grade ≥2R requiring specific therapy was detected in 44 (34%) patients. Those who suffered rejection experienced a mean of 1.8 ± 1.4 rejections ≥2R (range: 1–6 episodes; median: 1.0); mean time between OHT and first rejection grade ≥2R was 1.2 ± 2.4 years (range: 0.04–14.0 years). Rejection-free survival conditional to 20 years survival was 68 ± 4.1% at 5 years, 66.4 ± 4.2% at 10 years, and 65.6 ± 4.2% at 15 years (Fig. 2a).

Cardiac allograft vasculopathy

CAV grade 2 or 3 was diagnosed in 35 (27%) patients [CAV grade 2, n = 23 (18%); CAV grade 3, n = 12 (9%)]. CAV grade 2 or 3 appeared at a mean time of 14 ± 5.6 years (range: 1–23) after OHT. CAV-free survival conditional to 20 years survival was 97.7 ± 1.3% at 5 years, 93 ± 2.2% at 10 years, 87.6 ± 2.9% at 15 years, 76 ± 3.8% at 20 years and 72.1 ± 4% at 23 years (Fig. 2b). Thirty-one patients (24%) underwent one or more coronary angioplasty procedures with stenting, and no patient underwent coronary artery bypass grafting.

Malignancy

Malignancies were diagnosed in 69 (53%) patients and were multiple in 30 (23%). The most common type was

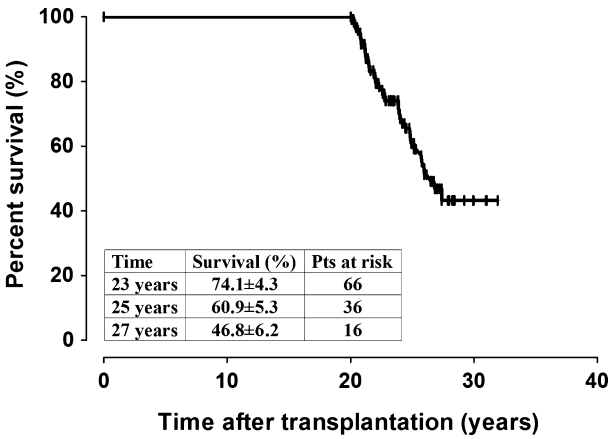

Figure 1 Survival after heart transplantation conditional to survival at 20 years.

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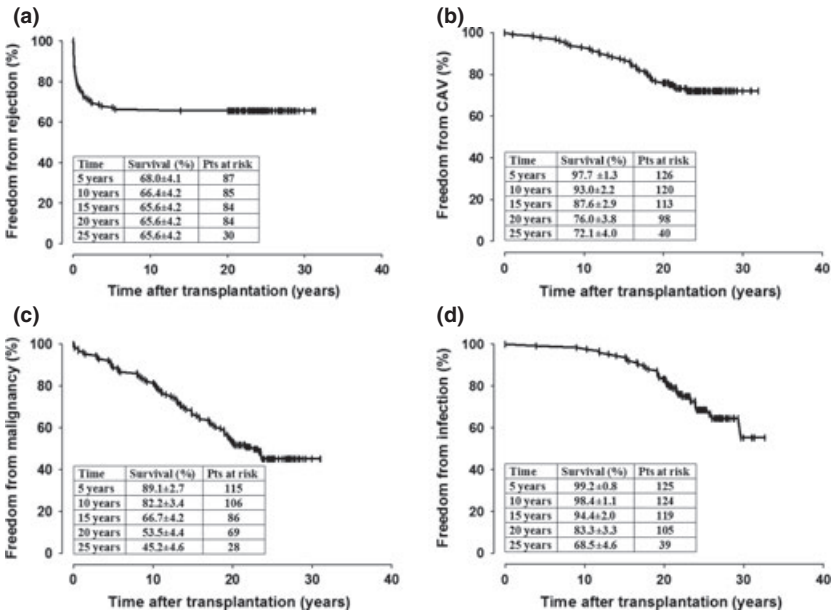

Figure 2 Transplant-related complications. (a) Rejection ≥2R-free survival; (b) Cardiac allograft vasculopathy grade 2- and 3-free survival; (c) Malignancy-free survival; (d) Infection-free survival.

skin malignancy [n = 39 (30%)], followed by nonlymphoid [n = 30 (23%)] and lymphoid malignancies [n = 17 (13%)]. Malignancy-free survival conditional to 20 years survival was 89.1 ± 2.7% at 5 years, 82.2 ± 3.4% at 10 years, 66.7 ± 4.2% at 15 years, 53.5 ± 4.4% at 20 years, 45.2 ± 4.6% at 25 years (Fig. 2c). Mean time between OHT and appearance of the first malignancy was 12.3 ± 6.7 years (range: 0.1–24).

Infection

Infections requiring hospitalization were detected in 42 (32%) patients and were multiple in 4 (3%). The most common infection was pneumopathy [n = 24 (18%)], followed by sepsis [n = 8 (6%)], hepato-biliary and bowel [n = 8 (6%)], urinary tract [n = 2 (2%)], cerebral [n = 2 (2%)] and skin [n = 1 (1%)] infection. Infection-free survival conditional to 20 years survival was 99.2 ± 0.8% at 5 years, 98.4 ± 1.1% at 10 years, 94.4 ± 2% at 15 years, 83.3 ± 3.3% at 20 years, 68.5 ± 4.6% at 25 years (Fig. 2d).

Clinical status at last follow-up

Follow-up was 96% complete as clinical records were lacking in 5 (4%) patients. The mean follow-up time after OHT reached 24.0 ± 3.0 years (range 20.1–31.9) with a median value of 23.4 years. At their last clinical evaluation, 122 (93%) patients were treated for hypertension, 27 (22%) for diabetes mellitus and 113 (86%) received statins. Fifty-one (39%) patients had chronic renal dysfunction (defined as a creatinine level >180 μM). Among these, 19 (15%) required haemodialysis and 8 (6%) patients had undergone renal transplantation. Eleven (8%) patients had experienced a cerebral vascular accident, 15 (11%) had peripheral vascular disease and 28 (21%) had a pace-maker.

The last echocardiography performed at a mean of 22.3 ± 2.7 years after OHT showed a left ventricular (LV) ejection fraction of 62 ± 11%, a LV end-diastolic-diameter of 49 ± 6 mm, a LV end-systolic diameter of 30 ± 5 mm, a septum thickness of 12 ± 2 mm and a tricuspid regurgitation of grade >2 in 9 (7%) of patients.

The immunosuppressive therapy at last follow-up is illustrated in Table 2. The immunosuppressive therapy after 20 years was unavailable in 5 (4%) patients. The most common immunosuppressive regimen consisted of a double therapy associating cyclosporine and corticosteroids in 67 (51%) patients while 58 (44%) patients received a triple

Table 2. Immunosuppressive regimen at latest follow-up.

Therapy	No. patients (n = 131)	Mean dose (mg/day)
Cyclosporine	119 (91%)	118 ± 52 (range: 30–300)
Corticosteroids	121 (92%)	9 ± 3 (range: 2.5–20)
Azathioprine	30 (23%)	29 ± 13 (range: 12.5–50)
Mycophenolate mofetil	25 (19%)	920 ± 387 (range: 500–2000)
Tacrolimus	5 (4%)	2 ± 1 (range: 1–4)
Everolimus	9 (7%)	1 (range: 0.5–1.75)
Sirolimus	1 (1%)	1

Table 3. Results of the SF-36 health survey in patients surviving more and less than 20 years after OHT.

SF-36 subscales	>20 years survivors (n = 81)		<20 years survivors (n = 52)		
	Mean ± SD	Median	Mean ± SD	Median	*P*
PF	61 ± 27	65	74 ± 24	80	0.006
RP	57 ± 40	75	66 ± 37	75	0.21
BP	61 ± 25	60	68 ± 25	78	0.11
GH	49 ± 18	52	59 ± 20	56	0.006
VT	49 ± 16	50	58 ± 19	60	0.004
SF	61 ± 27	62	77 ± 22	81	0.0007
RE	58 ± 43	66	69 ± 39	100	0.12
MH	63 ± 18	64	69 ± 16	72	0.05
PSC	57 ± 23	60	67 ± 22	73	0.003
MSC	58 ± 21	61	68 ± 20	75	0.001

Data are presented as mean ± SD and as median.
PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary.

therapy. No significant differences were found in actuarial survival (P = 0.11) and freedom from CAV (P = 0.96), malignancies (P = 0.11) or infection (P = 0.4) in patients receiving double or triple immunosuppressive therapy.

Quality-of-life assessment

Eighty-one (93%) more than 20 years survivors filled in entirely the SF-36 health survey at a mean of 23 ± 3 years after OHT and at a mean age of 65 ± 13 years. The remaining questionnaires were useless because of incompleteness or could not be filled in because of neurological diseases (i.e. Alzheimer's disease) or hospitalization or non-consenting patients. The mean scores of each SF-36 subscale were as follows: PF 61 ± 27, RP 57 ± 40, BP 61 ± 25, GH 49 ± 18, VT: 49 ± 16, SF 61 ± 27; RE 58 ± 43, MH 63 ± 18. The mean PCS score was 57 ± 23 (range: 14–98), and the mean MCS score was 58 ± 21 (range: 19–98) (Table 3). These data were compared to those from 52 less than 20 years survivors who completed the SF-36 health survey at a mean of 6 ± 5 years after OHT and at a mean age of 55 ± 12 years. The mean scores of each SF-36 subscale were as follows: PF 74 ± 24, RP 66 ± 37, BP 68 ± 25, GH 59 ± 20, VT: 58 ± 18, SF 77 ± 22; RE 69 ± 39, MH 69 ± 16. The mean PCS score was 67 ± 22 (range: 22–100), and the mean MCS score was 68 ± 20 (range: 16–98) (Table 3).

Discussion

To our knowledge, this is the largest series of long-term survivors after OHT ever reported. Twenty-year survival with a single graft was achieved by 16% of all transplant recipients at our institute after the introduction of cyclosporine in 1981 and by 26% of patients surviving the first year after transplant. Their estimated median survival reached 26.5 ± 0.8 years. These results agree with those from the Registry of the International Society for Heart and Lung Transplantation (ISHLT) which reported a 20-year survival rate of 21.6% and a 27% likelihood of being alive 20 years after transplantation for recipients who survived the first year [4]. To date, only few reports with a follow-up of more than 20 years after OHT have been published [7,12–14]. In the Stanford University experience, 60 (12.5%) patients transplanted between 1968 and 1987 survived 20 years or more and 11 of these long-term survivors had undergone re-transplantation [7]. This lower percentage of long-term survivors can probably be related to the earlier time period of their study, covering the precyclosporine area. On the other hand, median survival was slightly longer in the Stanford report than in our series (28.1 vs. 26.5 years), but this is likely due to younger recipients (mean age at transplant: 29 ± 14 vs. 42.9 ± 12.8 years) and donors (mean age: 22 ± 8 vs. 31.5 ± 12.3 years) in the Stanford cohort [7]. Other series reported 24% (12) and 26% (13) survival rates at 20 years in smaller cohorts. Recently, an excellent 20-year survival rate of 55% have been reported by Swiss authors (14), essentially due to the short ischaemic time related to the short distances between centres in their country and the high percentage of local in-house donors. This continuous survival improvement observed over the past three decades is essentially related to mortality reduction during the first postoperative year, and considerable improvement in long-term survival is also appreciable when compared with transplants performed between 1982 and 1992 [4].

Long-term survival was associated with serious morbidity. As shown in the present report, allograft rejection occurred mainly during the first 5 years after transplantation and did not significantly contribute to morbi-mortality thereafter. In contrast, CAV, malignancy and infection constituted a constant hazard during long-term survival and were the main causes of late deaths.

Although CAV-free survival was relatively high in our patient cohort, CAV accounted for the most frequent cause of late death, a finding similar to that from the Stanford group. In contrast, the ISHLT Registry reports that only 13% of late deaths occurring in 10 year survivors are related to CAV [4]. There are at least two explanations for this discrepancy. Approximately 10% of heart transplant recipients are diagnosed with CAV within 1 year after transplant and more than half of all recipients by 10 years after transplant [4]. Therefore, it is likely that 20 years after transplantation, the incidence and the severity of CAV are even higher. Furthermore, mortality due to CAV in the

international registry might be underestimated as 6% mortality denoted as 'graft failure' may, in reality, be related to unrecognized CAV [4].

In our series of long-term survivors, malignancy accounts for only 9% of deaths which is considerably lower than in other report [4,7]. Malignancies occurred in 53% of our recipients and 23% of them suffered from multiple lesions. However, the majority was represented by skin cancers, which have a lower impact on survival than hemopathies or solid organ tumours. Furthermore, according to our institution protocols, long-term survivors underwent at least a biannual check-up which allowed early detection of malignancies. Finally, most recipients received statin therapy which could reduce the incidence of malignancies and death for all causes after OHT [15].

Twelve patients (27%) died from septic shock, thus providing considerably higher infection-related mortality than that reported by the Stanford group (6%) or the ISHLT Registry (11%). These patients were relatively old (mean age 64.8 $\pm$ 11.7 years) and had serious comorbidities represented mainly by chronic renal dysfunction (6 patients were under haemodialysis and 1 had creatinine level >180 μM). Chronic renal dysfunction is relatively frequent in long-term transplant recipients. Thus, renal dysfunction defined as creatinine level >180 μM with or without the need for haemodialysis, and renal transplantation was noted in 45% of our recipients, which is similar to that from another report [7]. Renal dysfunction is well known to alter immune responses. Furthermore, immunosuppressive therapy is more difficult to equilibrate in patients with altered renal function, exposing patients to immunosuppressive drug overdose.

Our findings suggest that late events after transplantation are mainly related to long-term immunosuppression and to the immune interaction between the recipient and the allograft. The most common immunosuppressive regimen at last follow-up was a double therapy associating cyclosporine and corticosteroids in 51% of patients, while 44% of patients received a triple therapy. However, differences in immunosuppressive regimen did not significantly influence survival or actuarial freedom rates from CAV, malignancies or infection in our series.

Of note, long-term survivors of cardiac transplantation showed impressive cardiovascular hemodynamic function and good quality of life despite serious comorbidities. Thus, we observed a mean LV ejection fraction of 62% in 20 years survivors. Similarly, other series reported a mean LV ejection fraction of 58% and 59% in 10 and 15 years survivors, respectively. [16, 17] The mean PCS and MCS in patients surviving more than 20 years after OHT was significantly inferior than that of <20 years survivors. This could be related to the younger age and less comorbidities in recipients having survived <20 years. The mean scores of each SF-36 subscale in more than 20 years survivors were also inferior to that of the general French population. [18] However, our recipients had mean PSC and MSC scores above 50, indicating that patient perception of physical and mental health was similar to that of the general French population. Similarly, more than 10 years adult survivors after paediatric heart transplantation had mean PSC and MSC scores around 50 [19]. In contrast, a previous report focusing on quality of life in patients surviving more than 10 years after adult heart transplantation showed mean PCS and MCS scores of 45 and 49, respectively, with PCS significantly lower than the expected value of 50 for the general population [20].

In conclusion, 16% of patients transplanted from 1981 to 1992 survived more than 20 years and showed good LV performance and quality of life. Long-term survivors continue to develop fatal complications throughout the follow-up, dominated by CAV, malignancies and infection. Therefore, prevention, early diagnosis and appropriate treatment are essential to reduce long-term mortality. Nevertheless, advances in immunosuppressive therapy as well as in the understanding of immunological mechanisms are required to achieve further improvements in long-term survival after OHT.

Limitations of the study

The present study is a retrospective one, focusing on patients transplanted over a 13-year period dating 20–30 years back. Thus, completeness of data cannot be guaranteed, and the incidence of some postoperative events, such as infection, might have been underestimated. Furthermore, clinical records of patients who died more than 20 years ago were frequently lacking or incomplete, thus precluding our attempts to constitute a meaningful control group of patients transplanted during the same time period but who did not survive 20 years.

Authorship

AG: performed research/study, collected data, analysed data and wrote the paper. MK and SV: designed research/study, analysed data and wrote the paper. EB and FF: collected data. EV, AP and PL: analysed data.

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