In-hospital postoperative infection after heart transplantation: Risk factors and development of a novel predictive score

Paula Fernández-Ugidos[1], Eduardo Barge-Caballero[2,3], Rocío Gómez-López[4], María J. Paniagua-Martin[2,3], Gonzalo Barge-Caballero[2,3], David Couto-Mallón[2,3], Miguel Solla-Buceta[5], Carmen Iglesias-Gil[6], Vanesa Aller-Fernández[5], Miguel González-Barbeito[6], Jose Manuel Vázquez- Rodríguez[2,3], María G. Crespo-Leiro[2,3]

[1] *Servicio Medicina Intensiva, Complexo Hospitalario Universitario Ourense, Ourense, Spain*

[2] *Unidad de Insuficiencia Cardiaca y Trasplante cardiaco, Servicio Cardiología, Complexo Hospitalario Universitario A Coruña (CHUAC), INIBIC, UDC, A Coruña, Spain*

[3] *Centro de Investigación Biomédica en Red de enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain*

[4] *Hospital Quirónsalud Miguel Domínguez, Pontevedra, Spain*

[5] *Servicio Medicina Intensiva, CHUAC, A Coruña, Spain*

[6] *Servicio Cirugía Cardiaca, CHUAC, A Coruña, Spain*

Correspondence

Paula Fernández Ugidos, Servicio Medicina Intensiva, Complexo Hospitalario Universitario Ourense, Ourense, Spain. Email: paulaugidos@gmail.com and

Eduardo Barge-Caballero, Unidad de Insuficiencia Cardiaca y Trasplante cardiaco, Servicio Cardiología, Complexo Hospitalario Universitario A Coruña (CHUAC), INIBIC, UDC, A Coruña, Spain.Email: Eduardo.barge.caballero@sergas.es

Abstract

Introduction. Infection is one of the most significant complications following heart transplantation (HT). The aim of this study was to identify specific risk factors for early postoperative infections in HT recipients, and to develop a multivariable predictive model to identify HT recipients at high risk.

Methods. A single-center, observational, and retrospective study was conducted. The dependent variable was in-hospital postoperative infection. We examined demographic and epidemiological data from donors and recipients, surgical features, and adverse postoperative events as independent variables. Backwards, stepwise multivariable logistic regression with a P-value < 0.05 was used to identify clinical factors independently associated with the risk of in-hospital postoperative infections following HT.

Results. Six hundred seventy-seven patients were included in this study. During the in-hospital postoperative period, 348 episodes of infection were diagnosed in 239 (35.9%) patients. Seven variables were identified as independent clinical predictors of early postoperative infection after HT: history of diabetes mellitus, previous sternotomy, preoperative mechanical ventilation, primary graft failure, major surgical bleeding, use of mycophenolate mofetil, and use of itraconazole. Based on the results of multivariable models, we constructed a 7-variable (8-point) score to predict the risk of in-hospital postoperative infection in HT recipients, which showed a reasonable ability to predict the risk of in-hospital postoperative infection in this population. Prospective external validation of this new score is warranted to confirm its clinical applicability.

Conclusions. In-hospital postoperative infection is a common complication after HT, affecting 35% of patients who underwent this procedure at our institution. Diabetes mellitus, previous sternotomy, preoperative mechanical ventilation, primary graft failure, major surgical bleeding, use of mycophenolate mofetil, and itraconazole were all independent clinical predictors of early postoperative infection after HT.

Keywords

Heart transplantation, itraconazole, mycophenolate mofetil, nosocomial infection, postoperative infection, preoperative mechanical ventilation, primary graft failure, risk factors

1 INTRODUCTION

Heart transplantation (HT) is the therapy of choice for patients with refractory heart failure.[1] In selected candidates, HT confers good long-term survival, quality of life, and functional capacity.[1,2] However, the benefits of this therapy may be limited by post-transplant complications, such as rejection and infection, which are the most common adverse events.[3]

An infection can occur at any time after HT. Immunosuppressive therapy, previous rejection episodes, hypogammaglobulinemia, Cytomegalovirus (CMV) reactivation, prolonged hospital stay, preoperative cardiogenic shock, prolonged mechanical ventilation, and multi-organ transplantation have been described as potential risk factors for infection following HT.[3-8] Most studies have focused on the occurrence of post-transplant infections, in the long-term, but little data exists on infections that occur during the early postoperative period. Despite this fact, hospital acquired infections are known to be one of the leading causes of early postoperative death among HT recipients.[9, 10]

The aim of the present study was to identify specific risk factors for early postoperative infections in HT recipients (defined as any clinically relevant infection during the in-hospital period), and to develop a multivariable predictive model to help clinicians identify HT recipients at high risk for developing an infection.

2 METHODS

2.1 Study description

We conducted a single-center, observational, and retrospective study using a cohort of patients who underwent orthotopic HT in the Complejo Hospitalario Universitario de A Coruña (A Coruña, Spain), from April 1991 to December 2015. Patients younger than 18 years of age and those who did not survive the transplant surgery were excluded from the study.

The data for this study were collected from a prospectively maintained database and completed based on an individualized review of clinical records. The study protocol was approved by the Committee for Ethics in Clinical Investigation of the Autonomous Community of Galicia.

2.2 Clinical protocol

Using the bicaval technique, HT has been routinely performed at our institution since 1994. According to our institution´s protocol all patients received induction therapy, unless contraindicated. Muronab-CD3 was the preferred agent until 2001, and from then on, basiliximab was used routinely.

Maintenance immunosuppressive regimens included a combination of a calcineurin inhibitor (cyclosporine A or tacrolimus), an antiproliferative agent (azathioprine or mycophenolate mofetil) and corticosteroids. In patients with coronary allograft vasculopathy, severe renal failure, refractory rejection or post-transplant malignancy, an m-TOR inhibitor — sirolimus or everolimus — was used beyond the first post-transplant year instead of a calcineurin inhibitor or an antiproliferative agent. Mycophenolate mofetil, tacrolimus, and m-TOR inhibitors were used in our program in 1998, 2000, and 2005, respectively.

A chemoprophylaxis against opportunistic infections was used in patients undergoing HT in our institution. Perioperative antibacterial prophylaxis with cefazolin or vancomycin was administered.[11] All patients received an oral chemoprophylaxis against *P jirovecii*, trimethoprim-sulfamethoxazole (800/160 mg daily), for a minimum of 12 months after HT. Between 1994 and 2004, patients were treated with oral itraconazole (200 mg daily) during the first 3 months after HT for the prevention of pulmonary aspergilloses, but more recently, inhaled amphotericin B (50 mg weekly) has been used for this purpose. Patients with a positive purified protein derivative (PPD) skin test, prior to HT, were treated with oral isoniazid, 600 mg daily for 12 months after surgery, to prevent tuberculosis. Oral pyrimethamine (25 mg daily) was administered, during the first 6 months after HT, to recipients with a negative pre-transplant serology against *T gondii*.

Finally, oral valganciclovir (450-900 mg daily), for the prevention of CMV infection, was prescribed to all recipients during the first month after HT, after which, valganciclovir was switched to oral acyclovir (200 mg every 8 h), which was maintained for 3 months to prevent a *Herpes Simplex* infection. In the case of CMV seronegative recipients who received a CMV seropositive donor, oral valganciclovir therapy was extended until 6 months, post-transplantation.

2.3 Variables

In-hospital postoperative infection was the dependent variable in this study, which was defined as any clinically relevant infection occurring after HT and before the first hospital discharge of the patient. The diagnosis of every specific type of infection was made according to the clinical criteria of the attending physician, recorded in the patient's clinical history and confirmed by 2 independent investigators. Any discrepancies among the 2 independent investigators were resolved according to consensus criteria of the Infectious Disease Society of America.[12-14] Definitions of sepsis, severe sepsis, and septic shock were stated following the consensus criteria of the Surviving Sepsis Campaign.[15]

We studied demographic and epidemiological data from donor and recipients, surgical features, and adverse postoperative events as independent variables.

2.4 Statistical analysis

Descriptive analysis of qualitative variables was performed using Chi-squared and Fischer´s exact tests, whereas descriptive analysis of quantitative variables was performed using the Student's *t* test.

Backward stepwise multivariable logistic regression with a P-value < 0.05 was used to identify clinical factors independently associated with the risk of in-hospital postoperative infections following HT. Variables entered in the first step of this analysis were all those that showed a univariable association with the risk of in-hospital postoperative infection, with a P-value < 0.10, as well as the age and sex of the recipient. The 7 variables that retained a statistically significant, independent association

with the risk of in-hospital postoperative infection at the last step of the backward stepwise process formed the final multivariable model.

The Hosmer-Lemeshow test was used to assess the internal calibration of the multivariable predictive score. Categories of risk with several patients lower than 5 were assimilated to the closest category. The area under the receiver-operator curve ("*c* statistic") was used to determine the discriminative capacity of the model. The Chi-squared test was used to compare the observed and the predicted probabilities of infection across categories of risk.

Kaplan-Meier survival analysis and Cox´s regression were used to assess the cumulative incidence of in-hospital postoperative infection during the early postoperative period across categories of risk, as defined by the score punctuation assigned to each individual patient. A P-value < 0.05 was considered statistically significant for all contrasts. Statistical analysis was performed with SPSS 20.0.

3 RESULTS

3.1 Description of patients and in-hospital postoperative infections

From April 1991 to December 2015, 726 patients underwent HT at the Complejo Hospitalario Universitario de A Coruña (A Coruña, Spain). After the exclusion of patients less than 18 years of age (N = 35) and patients who died intraoperatively (N = 14), the study population included 677 patients.

During a mean in-hospital postoperative period of 25.4 ± 37.3 days, after HT, 348 episodes of infection were diagnosed in 239 (35.9%) patients, of which 175 (50.3%) of these episodes occurred during the stay in the Intensive Care Unit and 171 (49.7%) episodes occurred during the stay in the conventional ward. The sites and causal agents of the first episode of in-hospital postoperative infection diagnosed in these patients are listed in Table **1**.

3.2 Clinical characteristics of patients with or without postoperative infection

Table **2** shows a comparison of baseline clinical characteristics of patients who experienced at least 1 episode of in-hospital postoperative infection after HT and patients who did not. Statistically significant differences between patients with or without infection were observed with regard to diabetes mellitus, chronic renal failure, chronic liver dysfunction, malignancy, previous cardiac surgery, previous hospitalization, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, invasive therapies before transplant (mechanical circulatory devices, vasoactive drugs, mechanical ventilation, central venous catheter, and urinary catheter), previous infection, second heart transplantation, multi-organ transplantation, emergency heart transplantation, cardiopulmonary bypass time, primary graft failure, excessive surgical bleeding, redo surgery, transfusion, and immunosuppressive regimens.

3.3 Risk factors for infection

Table **3** shows the results of the logistic regression analysis designed to identify pre-transplant clinical characteristics associated with early postoperative infection following HT. Only variables that showed a univariable statistical association with the event of interest with, a *P*-value < 0.10 are presented.

Seven variables retained a statistically significant, independent association with in-hospital postoperative infection after backward stepwise multivariable logistic regression analysis. Three of them were clinical pre-transplant characteristics of the recipient (history of diabetes mellitus, previous sternotomy and preoperative mechanical ventilation), 2 were adverse operative events (primary graft failure and major surgical bleeding), and 2 were post-transplant therapies [use of mycophenolate mofetil (vs azathioprine/no antiproliferative agent) and use of itraconazole (vs Amphotericin B/no antifungal prophylaxis)].

3.4 Temporal trends of in-hospital postoperative infection

The cumulative probability of in-hospital postoperative infection following HT increased over time (1991-1999:29.5%, 2000-2007:39.6%, 2008-2015:40.1% P = 0.021), as did the prevalence of preoperative mechanical ventilation (1991-1999:6.4%, 2000-2007:16%, 2008-2015:12.1%; P = 0.002), diabetes mellitus (1991-1999:11.9%, 2000-2007:14.7%, 2008-2015:26.8%; P < 0.001), excessive surgical bleeding (1991-1999:13.3%, 2000-2007:19.1%, 2008-2015:34%; P < 0.001), primary graft failure (1991-1999:19.7%, 2000-2007:17.8%, 2008-2015:34.6%; P < 0.001), and mycophenolate mofetil use (1991-1999:14.6%, 2000-2007:87.9%, 2008-2015:95.5%; P < 0.001). Itraconazole use decreased over time (1991-1999:61.6%, 2000-2007:66.2%, 2008-2015:19.1%; P < 0.001, while the prevalence of previous sternotomy remained unchanged (1991-1999:24.7%, 2000-2007:30.2%, 2008-2015:29.3%; P = 0.332).
When the covariate era was added to the multivariable logistic regression model, there was no statistically significant effect on the risk of infection (OR era 2 vs era 1 = 0.84, 95% CI 0.49-1.49; OR era 3 vs era 1 = 0.84, 95% CI 0.41-1.69).

3.5 Predictive score

Based on the results of the multivariable analysis above, we created an 8-point score to predict the risk of in-hospital postoperative infection following HT. We assigned 2 points of risk to pre-transplant mechanical ventilation and 1 point of risk to each of the remaining 6 variables identified by multivariable logistic regression as independent predictors of in-hospital postoperative infection. The double weight of mechanical ventilation was justified because this predictor was the individual component of the score that showed the strongest association with the risk of infection, showing a multivariable OR of 3.674, while the OR of the other components ranged from 1.564 to 2.583.

As shown in Figure **1**, a close correlation between the expected and the observed probability of in-hospital postoperative infection was observed across categories of predicted risk. A numerically relevant deviation of the predicted risk of infection as compared to the observed risk was only noted in patients with a score of 0 points (predicted: 11%, observed: 16.9%; risk ratio = 0.65), however, this underestimation was not statistically significant ($P = 0.109$). The multivariable predictive model showed a good internal calibration, according to the results of the Hosmer-Lemeshow test ($P = 0.580$).

According to the receiver-operator curve, which is depicted in Figure **2**, the model showed a moderate-to-high capacity to discern patients at risk for in-hospital postoperative infection following HT (C-statistic 0.74, 95% CI 0.69-0.78).

3.6 Event-free survival curves

Figure **3** shows the cumulative risk of in-hospital postoperative infection over a 4-week follow-up period after HT, as estimated by the Kaplan-Meier curve, in patients with low (0-1 points), medium (2-3 points), and high (≥4 points) risk of infection according to our risk score. A statistically significant, increase in risk across groups was observed according to the logrank test for linear trends ($P < 0.001$).

Considering the low-risk group (0-1 points) as the reference category, the hazard ratio for in-hospital postoperative infection, as estimated by Cox´s regression, was 1.89 (95% CI 1.32-2.71) for patients of the medium-risk group (2-3 points) and 5.12 (95% CI 3.52-7.45) for patients of the high-risk group.

4 DISCUSSION

In this retrospective, single-center cohort study, we observed a cumulative incidence rate of 35% for in-hospital postoperative infection following HT. Roughly more than one half of the episodes of infection occurred during the early postoperative stay in the Intensive Care Unit. Respiratory and urinary tracts were the more frequent sites of in-hospital postoperative infections. In-hospital acquired microbial agents accounted for the vast majority of infections, while typical transplant-related opportunistic infections were relatively infrequent.

The incidence and localizations of postoperative infections observed in our population were, in general, consistent with reviewed literature,[16-19] as the reported incidence of postoperative infections varied from 22% to 70% or more in previously published reports.[4,16,20,21] Differences in the era addressed clinical criteria used to define infection and local protocols of immunosuppression and chemoprophylaxis may account for this apparent variability of results among studies.

The major focus of this study was to describe clinical predictors of in-hospital postoperative infection in HT recipients. Using multivariable models, 3 recipient-related conditions (previous cardiac surgery, diabetes mellitus, and the need for preoperative mechanical ventilation), 2 surgery-related complications (primary graft failure and excessive surgical bleeding), and 2 pharmacological regimens (the use of mycophenolate mofetil and the use of itraconazole) were identified as independent risk factors for postoperative infection in our cohort.

There is a well-established association between diabetes mellitus and the risk of postoperative infection,[22, 23] especially with a surgical wound.[24] Diabetes mellitus is a systemic disorder that favors a pro-inflammatory state and immunosuppression.[25] Moreover, diabetes mellitus has been described as a risk factor for graft failure in HT recipients.[26] Mechanical ventilation, especially for a long duration, is associated with a significant risk of nosocomial respiratory infections. Intubated transplant candidates frequently require other supportive invasive therapies like dialysis or mechanical circulatory support, which are also associated with an increased risk of infection.[7, 27] Both reasons might explain why preoperative mechanical ventilation was the strongest predictor of early postoperative infection in our population, with an adjusted OR of 3.67.

Previous cardiac surgery increases the challenge of HT surgery, and it is associated with increased risk of surgical bleeding, an increased need for blood transfusions, prolonged cold ischemic times and longer duration of cardiopulmonary bypass support,[28] in addition to, increased incidence of primary graft failure and postoperative infection,[19,29] as well as a longer hospital stay.[17] In our study, excessive surgical bleeding and primary graft dysfunction[7,19,30] were also identified as independent risk factors for early postoperative infection following HT.

Immunosuppressive therapy is a major determinant in the risk of infection in HT recipients.[8,31,32] In our population, the use of mycophenolate mofetil was independently associated with increased incidence of early postoperative infection. This result may be explained by the greater effect of immunosuppressive regimens that include mycophenolate mofetil in comparison to azathioprine-based or antiproliferative agent-free regimens. A strong correlation between steroid use and dosage, and the risk of infection after transplantation has been reported in previous studies.[7,9,17] However, we did not observe a significant correlation, possibly because all HT recipients in our study were treated with high-dose steroid therapy during the early postoperative period, as per our protocol.

We observed a statistically significant, increased risk of early postoperative infection among HT recipients who received oral itraconazole as an antifungal prophylaxis compared with those managed with amphotericin B or no antifungal drugs. While this result was unexpected, we hypothesize that the use of itraconazole might increase the risk of infection through increased bioavailability, and therefore, an increased immunosuppressive effect of calcineurin inhibitors.[33,34] Also, an in vitro study suggested that itraconazole is itself a potent inhibitor of the proliferation of T-lymphocytes,[35,36] but a significant clinical consequence of this phenomenon was never demonstrated. Further specific studies are needed to confirm the potential association of itraconazole use and increased risk of postoperative infection in heart transplant recipients; any case, a close monitoring of serum levels of calcineurin inhibitors is mandatory in candidates treated with this combination of drugs.

Ventricular assistance devices, transplantation in emergent situations and combined transplantation or re-transplantation showed a relationship with the development of infection in the univariate analysis, but not in the multivariate analysis, as in other studies.[6,7,20] Perhaps this difference between our study and other studies is because our sample size was not large enough to achieve sufficient statistical power.

Based on the results of the multivariable models, we constructed a 7-variable (8-point) score to predict the risk of in-hospital postoperative infection in HT recipients. The internal validation of the predictive score showed a good calibration across risk categories within the study population, except for the moderate underestimation of the real incidence of the event of interest in the lowest category of predicted risk (ie,

candidates with a score of 0 points). This result suggests the potential existence of other clinical factors that could account for additional risks of infection in HT recipients that could not be identified by our analysis. Regardless, it is notable that the score demonstrated a good capability to categorize patients at low, moderate, or high risk for infection, as demonstrated by the receiver-operator curve analysis.

From a clinical point of view, the main interest of our score is that it might help clinicians to refine the early therapeutic management of HT recipients. For example, in a patient in whom a high risk of postoperative infection is anticipated, the attending physician could consider initiating a less intense immunosuppressive regimen during the immediate postoperative phase, mostly if a high risk of rejection is not expected. Closer surveillance and more aggressive therapeutic management of infective complications is also warranted in these individuals. Patients at a high risk for infection may benefit from the serial determination of procalcitonin, presepsin, or proadrenomedulin levels as markers of infection, as these levels may rise before initial signs and symptoms of an infection are present.[37,38]

The results of our study reinforce the importance of some medical practices that can reduce the risk of postoperative infection after cardiac surgery, such as tight perioperative glycaemic control in diabetic patients, the avoidance of unnecessary blood transfusions or early postoperative weaning from mechanical ventilator support. Finally, the incidence of postoperative infection is a useful, quality metric for surgical teams. Large deviations in the observed rates of infection compared to predicted rates should lead to further investigations to identify and to correct the underlying reasons for these deviations.

This study has several limitations. First, it is a retrospective investigation, so it might be affected by selection, information, and confusion biases. It is especially notable that the definition of the type, cause, and site of infective episodes were essentially based on the clinical criteria of the attending physician. Second, the study had an intermediate sample size, which may not have provided sufficient statistical power to identify some other potentially relevant, but probably less strong, clinical predictors of early postoperative infection after HT. Third, the study addressed a long period of time, over which immunosuppressive and prophylaxis regimens have changed significantly, possibly affecting the overall incidence of postoperative infections. Finally, even though our

score showed a reasonable calibration and discriminative accuracy in the study population, its predictive ability must be confirmed through external validation in a different, contemporary, and prospective cohort.1.

5 CONCLUSIONS

Our study showed that in-hospital postoperative infection is a frequent complication following HT, affecting 35% patients who underwent this procedure at a single institution. Based on multivariable models, we developed a 7-variable (8-point) score which showed a reasonable ability to predict the risk of in-hospital postoperative infection in this population. A prospective, external validation of this new score is warranted to confirm its clinical applicability.

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AUTHORS CONTRIBUTION

Paula Fernández Ugidos: Data collection, conception of research, and manuscript drafting. Eduardo Barge Caballero: Conception of research, manuscript drafting, and statistical analysis. Rocío Gómez López: Data collection, manuscript review, and editing. María J Paniagua Martin: Manuscript review and editing. Gonzalo Barge Caballero: Manuscript review and editing. David Couto Mallón: Manuscript review and editing. Miguel Solla Buceta: Manuscript review and editing. Carmen Iglesias Gil: Manuscript review and editing. Ana Vanesa Aller Fernández: Manuscript review and editing. Miguel González Barbeito: Manuscript review and editing. Jose Manuel Vázquez Rodríguez: Manuscript review and editing. María G Crespo Leiro: Supervision, manuscript review, and editing.

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Table 1. Infection sites and causal agents of the first episode of in-hospital postoperative infection in a cohort of 677 heart transplant recipients

Infection site	N (239)	%	Causal agent (N)
Respiratory tract	94	39.3	Unknown (49)
			Staphylococcus aureus (7)
			Coagulase-negative Staphylococcus (2)
			Escherichia coli (8)
			Pseudomonas aeruginosa (6)
			Candida spp. (2)
			Aspergillus spp. (6)
			Proteus spp. (1)
			Haemophilus influenzae (2)
			Klebsiella spp. (2)
			Enterobacter spp. (3)
			Toxoplasma spp. (2)
			Moraxella spp. (2)
			Rothia mucilaginosa (1)
			Polymicrobial (1)
Urinary tract	28	11.7	Unknown (4)
			Coagulase-negative Staphylococcus (1)
			Enterococcus spp. (3)
			Escherichia coli (12)
			Ps aeruginosa (4)
			Candida spp. (1)
			Proteus spp. (2)
			Morganella morganii (1)
Catheter-related bacteraemia	19	7.9	*Staphylococcus aureus* (1)
			Coagulase-negative Staphylococcus (13)
			Enterococcus spp. (2)
			Candida spp. (1)
			Citrobacter freundii (1)
			Propionibacterium acnes (1)
Primary bacteraemia	9	3.8	*Staphylococcus aureus* (2)
			Coagulase-negative Staphylococcus (1)
			Escherichia coli (3)
			Capnocytophaga (1)

			Polymicrobial (2)
Cholecystitis	2	0.8	Unknown (2)
Peritonitis	11	4.6	Unknown (3)
			Proteus spp. (1)
			Klebsiella spp. (1)
			Enterobacter spp. (1)
			Polymicrobial (5)
Mediastinitis	9	3.8	Unknown (3)
			Coagulase-negative Staphylococcus (1)
			Streptococcus spp. (2)
			Enterococcus spp. (1)
			Escherichia coli (2)
Surgical wound infection	5	2.1	Unknown (2)
			E coli (1)
			Pseudomonas aeruginosa (2)
Defibrillator pocket infection	2	0.8	Unknown (2)
Enterocolitis	7	2.9	Unknown (2)
			Candida spp. (1)
			Cytomegalovirus (4)
Phlebitis	1	0.4	Unknown (1)
Periodontal infection	1	0.4	Unknown (1)
Meningitis	3	1.3	Unknown (2)
			Treponema pallidum (1)
Skin and soft tissue infection	4	1.7	Unknown (1)
			Coagulase-negative Staphylococcus (1)
			Escherichia coli (1)
			Polymicrobial (1)
Esophagitis	5	2.1	*Candida spp.* (1)
			Herpes simplex (4)
Endocarditis	1	0.4	Unknown (1)
Flu-like syndrome	7	2.9	*Cytomegalovirus* (7)
Suspected systemic infection	31	13	Unknown (31)

Abbreviation: N, number of patients.

Table 2. Comparison of baseline clinical characteristics of patients who presented in-hospital postoperative infections after heart transplantation and patients who did not

	No infection (N = 438)	Any infection (N = 239)	*P*-value
Clinical history of the recipient			
Sex: Male	81.7%	86.6%	0.103
Age (y), mean ± standard deviation	54.41 ± 11.02	54.40 ± 11.57	0.988
Year of transplantation			
1991-1999	47.5%	36.4%	0.021
2000-2007	31.1%	37.2%	
2008-2015	21.5%	26.4%	
Ischemic heart disease	40.6%	42.7%	0.607
History of smoking	30.8%	34.3%	0.353
History of excessive alcohol intake (>40 g/d)	14.2%	15.9%	0.541
Diabetes mellitus	12.6%	23%	<0.001
Hypertension	25.6%	31.8%	0.084
Chronic renal failure	12.6%	21.3%	0.003
Peripheral artery disease	3.9%	5%	0.484
History of stroke	7.8%	5.4%	0.256
Autoimmune disorder	2.7%	3.8%	0.462
Chronic obstructive pulmonary disease	11.4%	11.3%	0.963
Chronic liver dysfunction	1.8%	4.6%	0.037
Malignancy	1.1%	3.8%	0.043
Defibrillator	15.8%	19.7%	0.197
Previous cardiac surgery	22.6%	36.8%	<0.001
Creatinine (mg/dL); mean ± SD	1.37 ± 0.81	1.54 ± 1.54	0.117
Bilirubin (mg/dL); mean ± SD	1.20 ± 0.78	1.33 ± 1.03	0.099
Cardiac index (l/min/m2); mean ± SD	2.20 ± 0.58	2.29 ± 0.62	0.101
Mean pulmonary artery pressure (mm Hg); mean ± SD	27.68 ± 10.64	30.27 ± 11.18	0.513
Pulmonary vascular resistance (Wood); mean ± SD	2.13 ± 1.24	2.21 ± 1.32	0.500
Preoperative characteristics			
Recipient hospitalized before transplant	32.2%	54.4%	<0.001
INTERMACS profile 1 or 2 before transplant	8%	24.7%	<0.001
Mechanical circulatory support before transplant	12.9%	34.8%	<0.001
Ventricular assist device	0.7%	3%	<0.001
Extracorporeal membrane oxygenator	0%	2.5%	<0.001

Intra-aortic balloon pump	12.1%	29.3%	<0.001
Vasoactive drugs before transplant	15.1%	33.1%	<0.001
Mechanical ventilation before transplant	5.7%	20.5%	<0.001
Active infection before transplant	6.4%	15.1%	<0.001
Central venous catheter before transplant	11.4%	29.7%	<0.001
Urinary catheter before transplant	13.2%	32.6%	<0.001
Characteristics of donors			
Cause of death			
Stroke	44.7%	42.7%	0.871
Head trauma	48.6%	50.6%	
Other	6.6%	6.7%	
Sex: Male	75.3%	72.4%	0.409
Donor with antibiotics	30%	31.2%	0.737
Donor with proven infection	10.3%	12.1%	0.459
Age (y); mean ± SD	36.2 ± 15.8	35.6 ± 14.6	0.616
ICU stay (d), mean ± SD	3.74 ± 7.15	3.85 ± 5.05	0.834
Transplant surgery			
Second heart transplantation	0.7%	2.9%	0.039
Multi-organ transplantation	2.7%	5.4%	0.075
Emergency heart transplantation	13.7%	35.6%	<0.001
Cold ischemic time (min), mean ± SD	183.1 ± 74.3	194.8 ± 81.6	0.066
Cardiopulmonary bypass time (min), mean ± SD	121.4 ± 39.9	130 ± 42.9	0.009
Primary graft failure	15.8%	34.7%	<0.001
Excessive surgical bleeding	8.8%	29.4%	<0.001
Surgical Reintervention	6.8%	18.4%	<0.001
Need for transfusion	55.1%	73.2%	<0.001
Immunosuppressive therapy			
Induction therapy	95.7%	97.9%	0.131
Muronab-CD3	54.1%	44.8%	
Basiliximab	40.6%	51%	
Daclizumab	0.7%	0.8%	
Thymoglobulin	0.2%	1.3%	
Baseline immunosuppression			
Cyclosporine A	78.7%	71.1%	0.027
Tacrolimus	18.5%	27.6%	0.006
Azathioprine	42.8%	32.2%	0.007
Mycophenolate mofetil	52.9%	66.5%	0.001
Everolimus or sirolimus	1.4%	0.8%	0.719

Anti-infectious chemoprophylaxis			
Surgical chemoprophylaxis	99.3%	99.2%	0.828
Cefazolin	95.8%	92%	
Vancomycin	2.3%	3%	
Other	1.2%	4.2%	
Post-transplant chemoprophylaxis			
Trimethoprim-sulfamethoxazole	88.4%	91.6%	0.184
Isoniazid	25.1%	21.3%	0.270
Pyrimethamine	8.2%	12.6%	0.069
Nystatin	95.2%	96.2%	0.534
Itraconazole	48.9%	61.1%	0.002
Amphotericin B	27.6%	32.2%	0.209
Ganciclovir	71.7%	80.8%	0.009
Acyclovir	10.7%	12.1%	0.580

Abbreviations: INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; SD, Standard Deviation.

Table 3. Risk factors for early postoperative infection after heart transplantation: univariable and multivariable logistic regression analyses

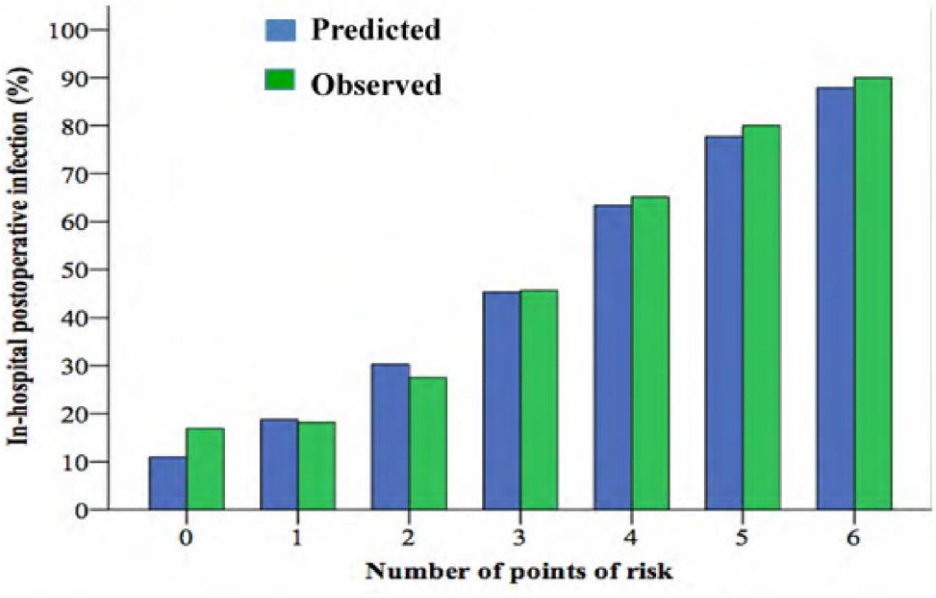
	Univariable analysis*			Multivariable analysis**		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Male recipient	0.69	0.444-1.079	0.104			
Age of the recipient (y)	1.00	0.986-1.014	0.988			
Diabetes mellitus	2.08	1.377-3.146	0.001	1.917	1.208-3.040	0.006
Chronic renal dysfunction	1.89	1.242-2.872	0.003			
Liver dysfunction	2.59	1.029-6.538	0.043			
History of malignancy	3.39	1.123-10.230	0.030			
Previous cardiac surgery	1.99	1.413-2.819	<0.001	1.564	1.060-2.309	0.024
Recipient hospitalized before transplant	2.51	1.817-3.473	<0.001			
INTERMACS profile 1 or 2	3.77	2.398-5.940	<0.001			
Mechanical circulatory support before transplant	7.78	2.572-23.563	<0.001			
Vasoactive drugs before transplant	2.78	1.911-4.052	<0.001			
Mechanical ventilation before transplant	4.26	2.555-7.105	<0.001	3.674	2.126-6.349	<0.001
Active infection before transplant	2.59	1.541-4.375	<0.001			
Central venous catheter before transplant	3.28	2.188-4.195	<0.001			
Urinary catheter before transplant	3.17	2.156-4.672	<0.001			
Second heart transplantation	0.23	0.059-0.892	0.034			
Emergency heart transplantation	3.48	2.378-5.084	<0.001			
Cardiopulmonary bypass time (min)	1.01	1.001-1.009	0.011			
Primary graft failure	1.93	1.540-2.413	<0.001	2.245	1.495-3.371	<0.001
Excessive surgical bleeding	4.30	2.780-6.662	<0.001	2.583	1.666-4.003	<0.001
Basiliximab use	1.52	1.109-2.092	0.009			
Tacrolimus use	1.67	1.155-2.433	0.007			

Mycophenolate Mofetil use	1.781	1.283-2.472	0.001	1.614	1.126-2.315	0.009
Itraconazole use	1.64	1.193-2.264	0.002	2.090	1.459-2.993	<0.001
Ganciclovir use	1.66	1.130-2.430	0.010			

Abbreviations: CI, Confidence Interval; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; OR, Odds Ratio.

* Variables presented are only those that showed a statistical association with in-hospital postoperative infection with a *P*-value < 0.10 in the univariable analysis.

** Coefficients presented are only those of variables that retained a statistically significant independent association (*P*-value < 0.05) with in-hospital postoperative infection in the last step of backward stepwise multivariable logistic regression analysis, and so, formed the final multivariable model.



N	65	165	207	116	66	45	10
Predicted (%)	11	18.8	30.3	45.3	63.4	77.7	87.9
Observed (%)	16.9	18.2	27.5	45.7	65.2	80	90
P/O ratio	0.65	1.03	1.12	0.99	0.97	0.97	0.97
p-value	0.109	0.842	0.365	0.852	0.798	0.720	0.935

Figure 1. Comparison of observed and predicted probabilities of in-hospital postoperative infection across risk categories. N: number of patients; P/O: Predicted/Observed

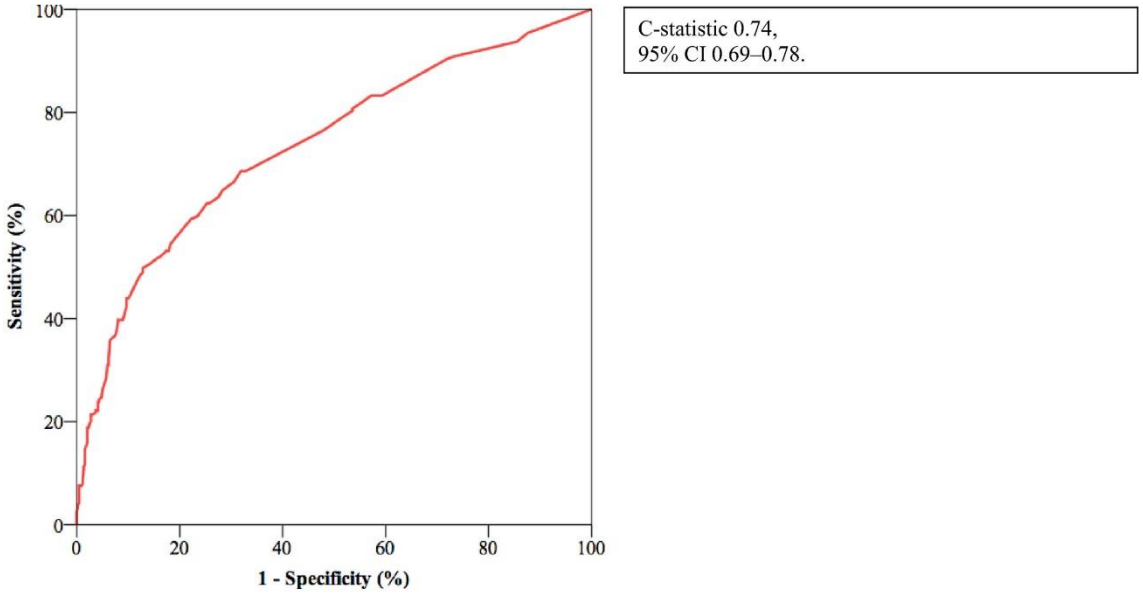


Figure 2. Accuracy of the proposed clinical score to predict the risk of in-hospital postoperative infection: receiver-operator curve

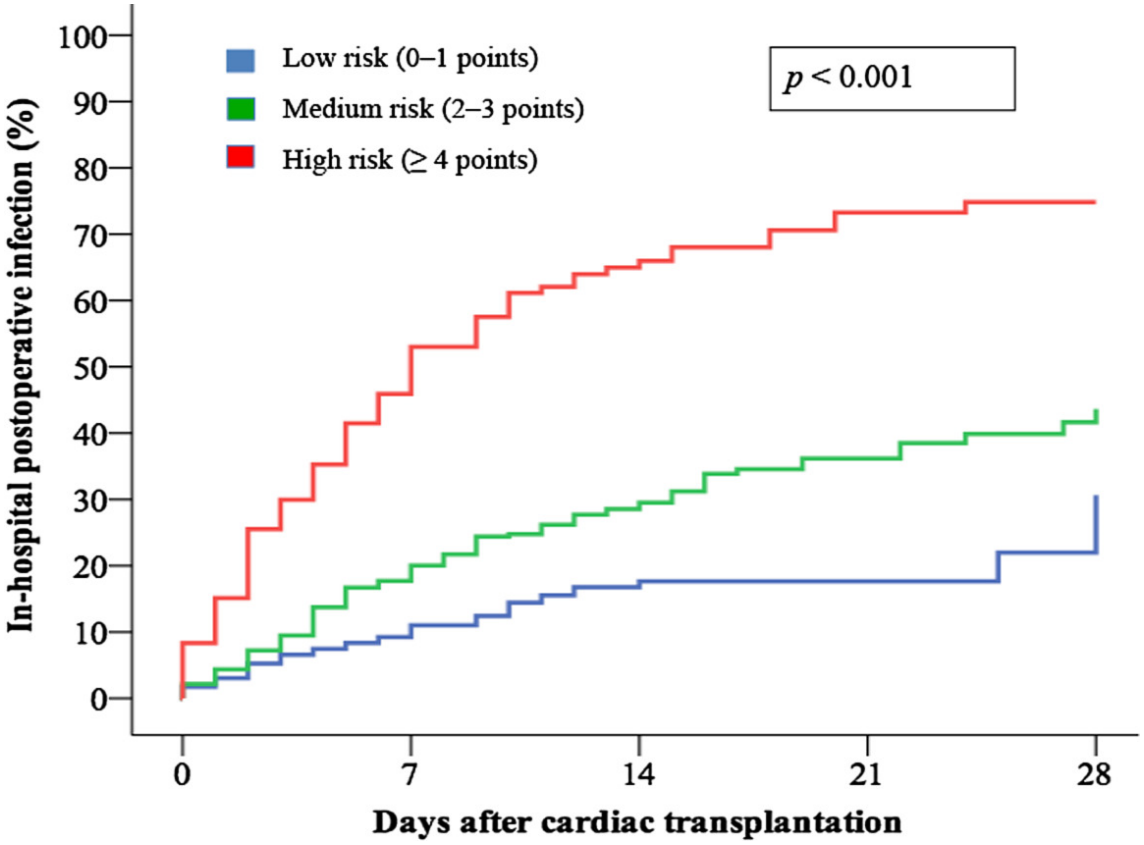


Figure 3. Cumulative incidence of in-hospital postoperative infection over the first 28 days after heart transplantation, across different levels of predicted risk