INTRODUCTION

Heart disease is the leading cause of death in the United States with an estimated 6 million adults living with heart failure[1]. Heart transplantation remains the gold standard for the treatment of end-stage and refractory heart failure. It is therefore indicated when the patient is under optimal medical therapy, has experienced multiple episodes of heart failure or acute events that have led to a loss of myocardial function with ou thope of recovery. Consequentially in selected candidates, heart transplantation (HT) confers good long-term survival, quality of life and functional capacity [2].

However, the benefits of this therapy may be limited by post-transplant complications, such as rejection and infection, which represent the most common adverse events 60-80% [3]. Substantial changes have recently occurred in the epidemiology of HT, including older patients and high priority assignments for critically ill patients [4-5].

Administration of immunosuppressive treatment is essential to prevent rejection, but these therapies expose the HT recipient to bacterial, viral, and fungal infections complications [6]. Infectious complications appear in 30–60% of HT cases [7], leading to death rates of 12–17% in the first month and 29–36% in the first year [8–9].

Although data on the epidemiology of postoperative infections remain limited, existing evidence indicate s that health care-associated infections are prevalent in the early post operative period following transplantation, similar to what is observed in general cardiac surgery. However, it is not uncommon for these infections to coincide with opportunistic infections as well [10]. Bacterial infections continue to be the most common type of serious infections [3,11-12], with Gram-positive organisms being the main infecting pathogens [6]. In cardiac surgery, the post operative pneumonia (POP) is still the most common infectious complication, it represent the 30% of the infection [13,14-15]. It'isknown to be associated with increate mortality [16]. POP incidence and risk factors, after HT, remain poorly studied [14]. A recent study indicates that pre-operative mechanical ventilation and blood transfusion appear to be risk factors for POP to increase mortality [15]

Furthermore, the latest studies have detected a cytomegalovirus (CMV) infection rate of 9–45% [16,17-18].

While the incidence and types of post-HT infections have been documented [8,3,12,13], the specific characteristics of patients who develop infections during the initial transplant period remain some what unclear. Descriptions of pathogens, sites of infection, and risk factors that contribute to early infection are lacking. Furthermore, the impact of early infection on clinical outcomes is unclear.The aim of this study is to analyze the epidemiology of post-operative infections and find risk factors for post-HT infections in order to try to prevent and better manage patients in the peri-operative period.

MATERIAL AND METHODS

1. Patients and settings

We conducted a single-center retrospective study between May 2015 and December 2023. All consecutive patients over 18 years of age who underwent a heart transplantat Pitié-Salpêtrière Hospital (Paris, France) were enrolled. Patients who underwent combined heart-kidney or heart-liver transplants and/or were hospitalized in another treatment center were excluded from the study. Patients are described in Table 1 and Table 1bis.

2. Endpoints

The primary endpoint was incidence of heart transplant infections. Secondary endpoints were

30-day, one-year and five-year mortality, duration of intensive care (ICU) stay for both infected and non-infected patients, duration of mechanical ventilation (for the entire population and for those who developed POP), dialysis, incidence of different infections and responsible germs, incidence of germs per infected site, BMR, POP, risk factors for the development of infection, identification of any opportunistic infections and their impact on mortality have also been studied.

3. Definitions

For the definitions and management of infectious complications were lied on Centers for Disease Control and Prevention (CDC) guidelines and expert recommendations [19-20].

The diagnosis of POP as definedat a clinical and imaging level by the presence of two or more signs et or symptoms including fever> 38.5° without other causes, withe blood cells (WBC) < 4000/mm3 or > 12000/mm3, recurrent purulent secretions or aspirations, recurrence or persistence of an outbreak on the chestx-ray, hypoxemia or increate oxygen requirements and at a microbiological level with the cultural positivity of bronchoalveolar lavage samples (positività threshold > 10^4 colony- forming-unit(CFU) /ml) or broncho-aspiration (10^6) and the PDP (> 10^3). We are definition ”early” pneumonie in case the infection arose in the first 5 days of hospitalisation and "late” in case after 5 days. Antibiotic therapy was continued for a maximum of 7 days. It was prolonged only in cases of certain situations (empyema, necrotizing pneumonia or abscess), while reduced to 5 days in case of early pneumonia (in the absence of foreign material and major comorbidities).

In the event that the respiratory samples were negative or below threshold, the benefit of the antibiotic therapy dipende on: the edges, failure to heal, general signs of infection (fever, leukocytosis), a sistemi inflammatory response syndrome in a patient on Extra Corporeal Membrane Oxygenation (ECMO) (or recently weaned) and of positive blood cultures in a patient in ECMO (or recently weaned) [21].

Mediastinitis was defined as a deep infection of the operative site (skin tissue and sternal osteomyelitis) by the presence of at least 1 criteria among: isolation of a germ by mediastinal sampling, evidence of mediastinitis surgical revision, chest pain with sternal instability, hyperthermia> 38 °C and purulent discharge or positive blood culture [22].

The diagnosis of urinary tract infections was made in the presence of clinical signs (fever > 38.5° or hypothermia, arterial hypotension, alteration of general status or lethargy without other causes) and microbiological signs. In the presence of an endourinary device were respected certain threshold values for the definition of infection [23].

CMV infection was defined as CMV virus detected by viral culture or quantitative PCR test for CMV in any sample of body fluid or tissue. CMV infection was defined as the first detection of CMV infection in an individual who had no evidence of CMV exposure before transplantation and was classified as CMV infection. CMV disease was defined as the presence of appropriate clinical symptoms and/or signs along with documentation of CMV in the tissues of the affected organ [24-25]. Herpessimplex virus (HSV) infection is established by quantitative PCR of the lower airways (viral load > 10^5 copies/million cells), identification of a cytopathogenic effect (giant, multinucleated cells, with specific nuclear inclusions) in the bronchoalveolar lavage (BAL) or lung biopsy [26].

Systemic fungal infection was based on positive blood cultures, direct examination and/or positive culture of normally sterile materials or tissues, PCR, and clinical findings (≥ 1 of the following 2 criteria after an episode of candide mia within the previous 2 weeks: hepatic or splenic abscesses or cerebral and retinal exudate or vitreous opacities on ophthalmological examination) [27-28]. The diagnosis of septic shock and sepsis were made

following the guidelines of the Suvival sepsis compaign [29]

4. Data collection

The data of the donors and recipients were retrieved from the medical records and from the Cristal database of the French Transplant Agency. The software used for data collection were Metavision® (IMDSoft, Wakefield, USA) and Orbis® (Agfa HealthCare, Mortsel, Belgique). In addition to the demographic, anthropometric and comorbidities parameters of the patients, many other parameters have been described. Among these, the duration of hospitalization, pharmacological and non-pharmacological support, infectious complications, sites, relapses with all the corresponding germs and mortalityat 30 days, 1 and 5 years stand out.

5. Patients management / HT protocol

Immunosupression

All recipients benefited from standard prophylactic immunosuppression according to our hospital protocol and according to the International Society of Heart and Lung Transplantation (ISHLT) [30]. Immunosuppression begins intra-operatively with an administration of 4 mg / Kg of methylprednisolone up on entry to the operating block, 120 mg during anesthetic induction and 120 mg after extra corporeal circulation (CEC). While in the post-operative period the patients received a quadruple therapy base donan tithymocyte globulins or basiliximab, corticotherapy, anticalcineurins and mycophenolate mofetil. In particolar antithymocyte globulins with a loading dose and a maintenance dose for three days by monitoring the daily dosage of lymphocytes and platelets or with basiliximab in the event that patients were infected or at high risk of infection or with a history of tumors and absence of donor specific antibodies (DSA) with loading dose in the immediate post-operative period and booster on day four; At fours day post-operative methyprednisolone 1 mg/kg/day or prednisolone, with progressive dose reduction starting from day 10 up to a maintenance dose of 0.3 mg/kg/day; At 2 day anticalcineurins, antithymocyte globulins in the first instance, at a dose of 0.01 mg/kg/day in continuous infusion with oral passage administration (PO) to 0.075 mg/kg/day divided into two administrations (target concentration 10-13 ng/ml for the first three months) or ciclosporin in case of intolerance to antithymocyte globulins, in the absence of renal failure (IR), at a dose of 1-2 mg/kg/day starting from day 2 in continuous infusion and conversion PO as soon as possible to 6 mg/kg/day divided into two administrations (concentrationat time 0 (T0) target 250-300 ng/ml for the first three months with adaptation to renal function and target after three months of 150 ng/ml); Mycophenolate mofetil 1g x 2/day (Intravenous IV or PO) starting from day 4 in case of WBC > 4000/mm3, 750mg x 2/day in case of 3000 < WBC < 4000/mm3 or no treatment with WBC <3000/mm3 (stop it if onset of an infection).

Antibacterial prophulaxis

Intraoperative antibioticprophylaxis was carried out using cefazolina at dose of 2 g before the sternal incision with a booster dose of 1 g every 4 hours until the end of the operation. In case of penicillin allergy, Vancomycin 20 mg/kg of actual weight was administered in continuous infusion with a maximum of 4 g and a booster dose of 10 mg/kg if duration longer than 8 h [31]. An exception is prophylaxis in case of systemic or rectal infection of BLSE/BHRe. For the latter, the ESCMID recommendations [32] were followed. Patients admitted to hospital before heart transplant surgery and those with LVAD received cefazolina at the same dosage as patients without hemodynamic support. Infectionl inked to a ventricular assist device did no trepresent a contraindication to transplantation except in cases

of septic shock. Patients with such infections had post-transplantant bacterial regimens and durations guided by the infectious immunocompromised host disease services consultation based on microbiology data and extent of infection (if present) observedat the time of LVAD explantation and orthotopic heart transplantation. In line generate the therapy was continued for two weeks in case of superficial infections (cavity orifice), for four to six weeks if deep infections (mediastinitis, device). In case of infection of the Implantable Cardiac Defibrillator, ICD lodge, antibiotic therapy was continued for two weeks while it was continued for 4-6 weeks in case of there werealso sistemi signs and/or positive blood cultures.

For all other infections were lied on expert warnings according to the guidelines proposed by SPILF and SFAR [31- 33]. Antibiotic prophylaxis was not continued post-operatively unles sactive or emerging infections were detected

Viral immuno prophylaxis

Both donors and recipients were screened for opportunistic infections (toxoplasmosis, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Human immunodeficiency virus (HIV), HepatitisB virus (HBV), Hepatitis C virus (HCV), Syphilis) [29]. In case of donator positif (D+) or negatif (D-) and receiving positif (R+), the CMVprotein c reactif (PCR) was carried out starting from day 7 and every monday for 4 months. Therapy with valganciclovir 900 mg x 2/day for three months was started in case of positive PCR and with > 10.0000 viral copies (4log) while for all the remaining cases it was sufficient to continue monitoring.

In case of D+ and R- the treatment was started starting from day 10 for three months.

Toxoplasma and Carinii pneumocystis immunoprophylaxis

Systematic treatment of D+/R-. Therapy based on Bactrim 100 mg/day starting from day 10, replaced by malacide in case of Bactrim allergy or leuko-neutropenia.

It was carried out systematically for the first year with Bactrim 100 mg/day starting from day 10 in case of the WBC > 2000 mm3.

6. Statistical analysis

Continuous variables were reported as means and standard deviations, categorical variables were reported as frequency and percentages. We used Student's t test or Mann-Whitney test to compare continuous variables of infected vs uninfected patients. While the $\chi 2$ test or Fisher test were used to compare categorical variables. Survival were tested with Kaplan-Meier curves and compared with the log-rank test. Stepwise logistic regression was applied to identify risk factors for postoperative infection. Variables significantly associated with infections at univariable analyses were included in the multivariable model. A p value <0.05 was set as significance level.

7. Ethics

This study was reported to the French data protection authority (CNIL). The study received the approval of our institutional ethics committee. The authorization was granted to waive informed consent, because the patients were treated according to standard procedures, and data were retrospectively analyzed.

RESULTS

A total of 311 heart transplanted and consecutively included patients from January 2015 and December 2023. 150 patients (48.2%) of patients experimented infections including sepsis, pneumonitis and surgical site infections during the intensive care unit (ICU) stay after surgery.

Enterobacteriaceae and Pseudomonas aeruginosa were the most common pathogens.

30-day mortality was significantly higher in patients with infections (17/150 [11.3%]) than without (8/161[5.0%], p=0.039). Figure 1

Similarly, 5-year survival after surgery was significantly higher for patients who do not develop postoperative infection (log-rank test p value<0.001).

Duration of hospitalization in intensive care (ICU), sub-intensive and in hospital, duration of mechanical ventilation day 28, CEC and assistance, intra- and extra-operative transfusions, post-operative bleeding within 24 hours of transplantation, duration of administration of catecholamines day 28 and nitric oxide, duration of dialysis day 28, high lactates and ASA were significantly associated with postoperative infections Figure 2.

At multivariable analysis, the risk factors for infection were ecmova (OR 2.60, 95%CI 1.30-5.03, p=0.006), DefaillanceP (OR 1.46, 95%CI 1.05-2.012, p=0.023), dureececsup (OR 1.81, 95%CI 0.98-3.32, p=0.06) and, dureesejourr (OR 1.17, 95%CI 1.12-1.22, p<0001).

Our study had an average age of 56 years, predominantly male (75.6%), with BMI 25 and 45% had already undergone cardiac surgery. 45% of patients had pulmonary hypertension, 18% were diabetic and 31.2% had chronic renal failure. 50% of patients of patients admitted to intensive care had 50% mortality (IGS2 / SAPS2 50.5%). Table 1.

Infections were confirmed to be the most frequent complications 48.2% in addition to sepsis 23.8%, after heart transplant together with primary graft dysfunction 83% (39.1% left ventricular dysfunction, 24.4% right ventricular dysfunction, 34.6% bi-ventricular dysfunction) , hemorrhagic shock 25.7%, septic shock 23.8%. The site mainly responsible for the infections was the lung 35%, followed by bacteremia 26%, SSI in particular mediastinitis 10% and shoe infection 8.4% and finally UTIs 2.6%.

The average length of stay in intensive care was 17.2 days with an increase in mortality and risk of infection. Significant risk factors also associated with an increase in mortality were the presence of ECMO, prolonged duration of hospitalization in intensive care and a high lactate value. The infections were mostly caused by Enterobacteria and pseudomonas aeruginosa with a presence of opportunistic germs in secondary infections. POP was confirmed to be the most frequent infection 36% followed by bacteremia and SSI.

DISCUSSION

Since the first heart transplant was performed >50 years ago, considerable progress has been made in reducing the risk of infection and improving infectious disease-related outcomes in heart transplant patients. This is largely due to increased globally shared knowledge of infectious diseases in the immunosuppressed host, the introduction and modification of antimicrobial prophylaxis regimens, advances in diagnostics, continued development of antimicrobial agents, and personalized immunosuppressive regimens. Over time, changes have occurred in the epidemiology of infectious complications in heart transplant patients. However, compared to other transplants, heart transplants appear to be associated with a lower risk of post-operative infection. Over the years, infections from resistant mule germs have increased, thus requiring the use of a second line of therapy, generally producing greater renal toxicity and generally greater systemic toxicity [34].

We conducted a large, single-center retrospective study to describe the epidemiology, risk factors, and infections occurring within 30 days after HT. We also assessed the 1-year and 5-year mortality after HT. To our knowledge, it is the largest single-center cohort of recent heart transplants in adult patients in which infections and their impact on prognosis have been analyzed. We found a very high rate of infections after HT n = 150 48.2%), mostly bacterial (n = 80, 71%). Furthermore, we identified factors associated with non-viral infections in the postoperative period: ECMO, CEC duration greater than 120 minutes, increased duration in resuscitation. According to

the literature, the cumulative incidence of infections following hormone therapy varies from 35 to 80%, depending on the definitions of infections and the choice of time interval after HT [14,16,35-36].

The most common bacterial and fungal infections in our study were pneumonia (36%) followed by surgical site infection SSI (8.7%) in agreement with the literature [14,16,4-5]. The microbiological spectrum of infections did not differ from previous studies. Enterobacteria are responsible for most bacterial infections [14,4,37]. In our study we did not evaluate the incidence of MDR bacteria which appear to increase in the years both before and after HT [14-38]

POPs represent the most frequent infectious complication. In our HT recipient study, POP occurred in 36% of patients and was mainly caused by Enterobacteria and Pseudomonas aeruginosa and consistently increased mortality 30 days and 5 years after transplantation. This result is confirmed by reading as Vidal et al (2020) recalls it with a POP rate of 33%. They identified pre-operative mechanical ventilation and post-operative transfusion to which post-operative bleeding was indirectly linked as the main risk factors. In our study we found: duration of hospitalization in intensive care, in sub-intensive care and in hospital, duration of CEC, mechanical ventilation, circulatory assistance, persistence of amines, NO, postoperative bleeding and the need for transfusion within 24 hours, the duration of dialysis and the ASA. Several authors have demonstrated that infections were the main cause of morbidity and mortality. They also demonstrated that late-onset POPs were more frequently caused by CMV, Aspergillus fumigatus and Pneumocystis carinii [39-3]. Allou et al and confirmed by other studies such as that of Vidal have demonstrated that the POP pathogens are the septic ones for other non-cardiac surgeries [40]. This must be remembered to set antibiotic prophylaxis.

Surgical site infections (SSI) are defined by the CDC definitions as superficial, deep and with organ involvement, in particular 3.9-16% for superficial infections, 2.4%-35% for deep infections, including mediastinitis. Sternal dehiscences are present between 12.5% and 25%. Mortality rises up to 35%.

Mediastinitis represents another infectious complication in the post-operative period. In our study the incidence rate was 10% and the most responsible germs were Streptococcus epidermidis and Candida. The data were confirmed by the literature. Abbo et al in their guidelines reported a frequency of 7% with consecutive increase in mortality. The major risk factors were age, obesity, diabetes mellitus (DM), previous cardiac operations and intracardiac device, prolonged ventilation, reoperation, time to diischemia of the transplanted organ, and colonization of the donor. Bacteria, in particular Staphylococcus spp, S.aureus including MRSA, enterococcus, enterobacteriaceae including ESBL, Pseudomonas aeruginosa, stenotrophomonas and Candida were mainly responsible germs [41].

In our cohort, the IEp rate was 0%. This figure could be influenced by retrospective bias. AShrit et al (2020) demonstrated an overall infection rate of 2.15 per patient, predominantly caused by bacteria (1.34 IEp per patient), followed by viruses (0.65 IEp per patient) and fungi (0.02 IEp per patient) [42].

We noticed that CMV infection was predominant in secondary infections especially in POP infections but with a lower percentage compared to the study conducted by Pons et all. [14]. This explanation could be answered by new therapies and new prevention protocols [43]. This aspect would seem positive as it has been seen that CMV infection is associated with a greater presence of allograft vasculopathy at 10 years and consequently with lower long-term survival [44,45].

Bacterial infections were associated with an increase in intensive care hospitalization and an

increase in mortality as well as hospitalization costs. This is confirmed by the literature [46].

In agreement with the literature, this study demonstrates that the presence of mechanical hemodynamic support and the need for early CRRT are the cause of greater post-operative infection [47]. In particular, it has been found that ECMO within 24 hours is a risk factor for infection. We did not find a significant increase in the incidence rate with the use of other hemodynamic supports. However, this may be tainted by too small a sampling, as only two patients had it. To our knowledge, there are no studies that demonstrate how impella and CPS implantation influence the rate of infectious complications.

However, conflicting studies on the LVAD. Some studies demonstrate that this does not increase the rate of post-operative infections and mortality [37], while others given the relative immunosuppressive state in patients with VAD, showing a greater incidence of hypogammaglobulinemia [48] and a decreased response to stimulation tests lymphocytic [49] after VAD implantation.

Bacteremia represents another infectious complication that usually arises within the first month post transplant and has a high mortality rate of 35%, increasing up to 59% if it progresses to septic shock, particularly if the outbreak is of pulmonary origin [50 - 51]. The incidence is 16% and the main origin is pulmonary 23%, urinary 20% and venous catheters 16%. The responsible germs are 55% G- bacteria Pseudomonas aeruginosa and Enterobacteria and 44% G+ including Staphylococcus aureus et epidermidis. Opportunistic infections of CMV, HSV and Candida stand out.

Urinary tract infections are the fifth source of infection. They occurred in 2.6% of cases and were mainly caused by Enterobacteria and E.Coli.

There are several limitations of this study. First of all, it is a retrospective study therefore it could represent an important source of bias for the identification of some information, for example for symptomatic CMV disease, such as symptoms such as diarrhea or it is possible that an isolated fever was not detected. Immunology protocols have changed over the years. Most positive cultures were identified during the patient's stay in the ICU, and the incidence and impact of an early positive culture outside of an ICU remain unknown. Pre-transplant infections of the devices were not reported due to incomplete information in the dossier. It is unknown whether prior infections, outside of chronic driveline infections, increased the risk of post-OHT infection in this study. Furthermore, it was not possible to evaluate the impact of the application of the nasogastric tube and enteral nutrition on the onset of pneumonia infections. Because this study was conducted at a single institution, the findings may not be applicable to other institutions.

However, the monocentricity of the study represents an important strong point. In fact, all patients were treated not only in the same hospital but in the same department because the patients admitted to other intensive care units had been deliberately eliminated from the study. Therefore the same protocol was applied to all patients. Another strong point is the homogeneity and size of the sample. Only patients who had received an ortho topical cardiac transplant were studied while those who had received multiple transplants were excluded. To our knowledge, it was the largest retrospective study in terms of sample size, although some patients were eliminated from the study due to incomplete information.
Surely in the future we would need a prospective study, which also considers previous infections and studies the correlation of germs with mortality.

CONCLUSION

In conclusion, this study has provided additional descriptions of the OHT patient population with

an infection in the early post-operative period. Gram-negative organisms accounted for the majority of isolates, with most common sites of infection being the lungs and SSI. Although no statistically significant differences in overall mortality, rejection, or re-admission rates were seen, a longer LOS and duration of mechanical ventilation were found in patients with an early infection. The relative difference in the 30-day anda 1 year mortality rate may support a modified approach to preventing infection in higher-risk patients. ECMO support and the need for long recovery period in the UTI may place heart transplant recipients at risk for an early infection. Evaluation of peri-operative antimicrobial prophylaxis duration and selection based on an individual center's resistance panels may be warranted in these

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Geographic characteristics	Patients (n=311)
Age	56 [48 – 63]
Gender, male n (%)	235 (75.6)
BMI	25.0 [22.7 – 28.4]
Previous heart surgery, n (%)	140 (45.0)
HTAP, n (%)	140 (45.0)
Diabete, n (%)	57 (18.3)
HTA, n (%)	90 (28.9)
IRC, n (%)	97 (31.2)
Chronic dialysis, n (%)	4 (1.3)
AOMI, n (%)	19 (6.1)
BPCO, n (%)	20 (6.4)
ASA	4 [4 – 4]
SOFA	10 [7 – 13]
IGS2 – SAPS2	50.5 [41.0 – 59.0]
Pre-operative creatinine	110 [88 – 140]

Table 1: IGS2 (*simplified severity index*) andSAPS2 (*Simplified Acute Physiology Score II*) :they are two scores that evaluate mortality 24 hours after admission to intensive care. They are based on 12 physiological variables and 3 disease-related variables with scores from 0 to 163 (0% and 100%

Per operative general characteristics	Patients (n=311)
Dobutamine, n (%)	65 (20.9)
Assistance	7(24.1)
LVAD	28 (9.0)
Artificial heart	5(1.6)
ECMO-VA	42 (13.5)
Pre-operative dialysis, n (%)	2 (0.6)
Infections	49 (15.8)
CEC duration	121 [102 - 146]
Cold ischemia time	201 [175 – 230]
Age donors	52 [40 – 59]
Weight donor	75 [65 – 86]

Table 1 bis: CEC duration = mean minutes; Cold ischemia time = mean minutes

Survival Curve

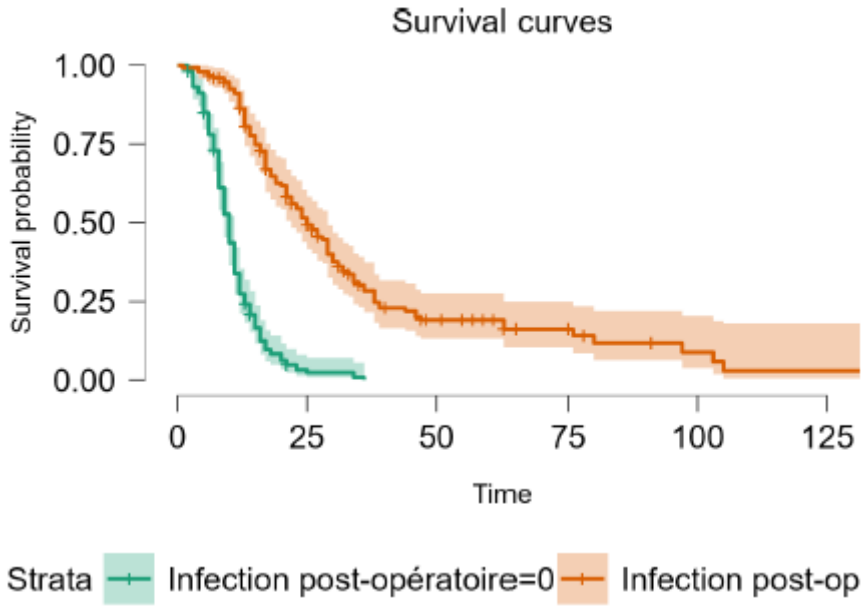

Figure 1

Test of Equality of Variances (Brown-Forsythe)

	F	df_1	df_2	p
age	3.851	1	309	0.051
bmi	0.379	1	309	0.538
dureesejourrea	55.228	1	309	< .001
dureesejourSI	13.730	1	238	< .001
dureevm	38.526	1	309	< .001
J28 - VM	90.693	1	309	< .001
dureesejourhop	10.562	1	309	0.001
Hbpreop	1.507	1	309	0.220
AgeDonneur	2.458	1	255	0.118
dureecec	12.368	1	308	< .001
dureeca	3.258	1	306	0.072
dureeassistance	5.061	1	308	0.025
dureeischemie	1.188	1	307	0.276
cgrperop	13.554	1	309	< .001
pfcperop	9.023	1	309	0.003
plqperop	4.535	1	309	0.034
retransfusionperop ml/kg	1.122	1	248	0.291
maxnoradreperop .g/kg/min	0.346	1	309	0.557
maxdobuperop	0.038	1	309	0.846
protatotperop (mg)	1.516	1	304	0.219
maxnoradrepostop .g/kg/min	1.224	1	309	0.269
dureenoradre	10.852	1	309	0.001
maxdobupostop	2.976	1	309	0.086
dureedobu	20.958	1	309	< .001
VISscoreH24	1.964	1	309	0.162
J28-catecho	46.722	1	308	< .001
dureeno	8.948	1	306	0.003
dureeecmo	32.976	1	307	< .001
saignpostop<12h ml/kg	6.543	1	309	0.011
saignpostop<24h ml/kg	6.517	1	309	0.011
cgrpostop< 24h	12.029	1	306	< .001
cgrpostoprea	68.152	1	306	< .001
dureeeer	89.456	1	309	< .001
J28 - EER	170.303	1	309	< .001
maxlacpostop	11.311	1	308	< .001
asa	5.998	1	309	0.015
igs2	1.677	1	308	0.196
sofa maximum	2.499	1	308	0.115

Figure 2