



## Mortality due to hospital-acquired infection after cardiac surgery

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**Mortality attributable to hospital-acquired infection after cardiac surgery.**

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**Access to data**

Data are available from corresponding authors on reasonable demand.

**Contribution**

CPC, JPV, NN and NM contributed to the acquisition of data. NN, and NM conducted the statistical analysis, contributed to the study conception and design as well as the analysis and interpretation of the data. NN, AM, JTR and NM drafted the manuscript, and all authors critically revised the manuscript and approved the final version.

**IRB number and date of approval**

The local IRB (« comité d'éthique du CHU de Rennes ») approved the study (N°19.53) the 12 of may 2019.

**Mortality attributable to hospital-acquired infections after cardiac surgery**

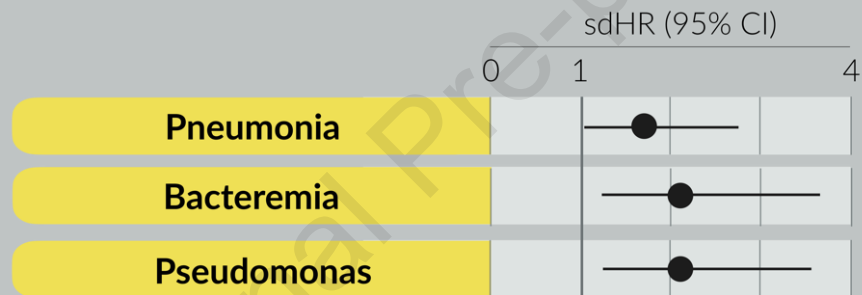
8,853 patients



Cardiac surgery



2012-2019

**Postoperative infections**  
4 %**Attributable mortality**  
17 %**In hospital mortality in patients with hospital-acquired****Low incidence but major impact on postoperative mortality**

1    **Central message :**

2    Patients with HAI after cardiac surgery have a higher risk for death, especially in patients  
3    with *Pseudomonas aeruginosa* infection, acquired bloodstream infection or acquired  
4    pneumonia.

5    **Perspective Statement :**

6    Few is known about HAI attributable mortality after cardiac surgery. We conducted a  
7    Propensity-score matched analysis that allowed the estimation of HAI attributable mortality  
8    fraction. Although few patients developed HAI (4.2%), attributable mortality fraction is high  
9    (17.1%).

10   **Abbreviated legend for Central Picture**

11   Mortality attributable to hospital-acquired infections (HAI) after cardiac surgery

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**ABSTRACT****Purpose:**

Hospital acquired infections (HAI) have been associated with significant morbidity and mortality in critically ill surgical patients. However, little is known about HAI-attributable mortality in cardiac surgery.

**Material and Methods:**

We conducted a retrospective analysis of prospectively collected data from the cardiac surgery unit of a university hospital. All patients who underwent cardiac surgery over a seven-year period were included. Patients with HAI were matched 1:1 with non-HAI patients based on risk factors for HAI and death after cardiac surgery, using propensity-score matching. We performed a competitive risk analysis to study the HAI-attributable mortality fraction.

**Results:**

Of 8,853 patients who underwent cardiac surgery, 370 (4.2%) developed 500 post-operative infections (incidence density rate 4.2 HAI per 1,000 patient-days). Crude hospital mortality was significantly higher in HAI patients than in matched patients who did not develop HAI, 15.4% and 5.7% respectively ( $p < 0.001$ ). The in-hospital mortality fraction attributable to HAI in our cohort was 17.1 % [12.3% – 22.8%]. *Pseudomonas aeruginosa* infection (HR = 2.09; 95% CI [1.23-3.49];  $p = 0.005$ ), bloodstream infection (HR = 2.08; 95% CI [1.19–3.63]  $p = 0.010$ ) and pneumonia (HR = 1.68; 95% CI [1.02–2.77];  $p = 0.04$ ) were each independently associated with increased hospital mortality.

**Conclusion:**

While HAIs are relatively uncommon after cardiac surgery (4.2%), these infections have a major impact on post-operative mortality (attributable mortality fraction 17.1%).

**Keywords:** Hospital-acquired pneumonia; Bacteremia; Surgical site infection; Mortality; Propensity score

## INTRODUCTION

Hospital-acquired infections (HAI) are a well-known source of morbidity in hospitalized patients but studies on attributable mortality have been confined to critically ill patients (1-7). The available literature suggests an increased mortality associated with HAIs, especially in patients with bloodstream infections or pneumonia, or in those with a surgical indication for admission (2-9). The association between death and HAI after cardiac surgery has been incompletely studied (10-21). Most studies focused on the identification of risk factors for HAI after cardiac surgery and concluded that HAI are directly related to patients' comorbidities, intraoperative factors, and postoperative management. A few studies assessed HAI attributable mortality, with confusing results, mostly due to potential confounders such as differences in baseline characteristics (for example comorbidities, age) or non evaluated risk-factors (for example type of surgery, length of cardiopulmonary bypass) or the method used for statistical analysis (for example multi state model, matched pair analysis) (10,13,17). Propensity score matching minimizes the influence of confounding factors, and is appropriate where only observational studies are feasible (6, 22). To our knowledge, this method has been used to estimate the attributable mortality of HAI in cardiac surgery patients only once, in a single center retrospective study that included only patients with a prolonged intensive-care-unit (ICU) stay. The authors concluded that HAI may increase death by 15 % (13).

We hypothesized that HAI after cardiac surgery are responsible for an increased mortality. Therefore we conducted an observational study with propensity-score matched analysis in order to assess the incidence, factors and outcomes associated with HAI in patients undergoing cardiac surgery. The primary objective was to determine the HAI-attributable mortality fraction. The secondary objective was to identify variables associated with death in patients with HAI after cardiac surgery.



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## 83 MATERIAL AND METHODS

### 84 Setting and Patients

85 We conducted a retrospective analysis of prospectively collected data, in accordance with the  
86 Strengthening The Reporting of Observational Studies in Epidemiology (STROBE)  
87 guidelines. The study took place in a French cardiovascular and thoracic surgery ward in a  
88 1,500 bed tertiary university hospital. Prospective data were collected routinely for all patients  
89 undergoing cardiac surgery as part of an ongoing quality improvement program. All patients  
90 who underwent open cardiac surgery from the 1<sup>st</sup> of January 2012 to the 31<sup>th</sup> of December  
91 2018 were screened and only patients without missing data were finally included. Patients  
92 were followed from the day of surgery until death or discharge from the hospital (including  
93 care in the ICU and non-ICU wards). A dedicated research nurse followed patients from  
94 discharge until one year after surgery. In hospital, caregivers followed the recommendations  
95 of the French Society for Hospital Hygiene regarding the prevention and treatment of HAI  
96 (available at <https://sf2h.net>). As part of our institutional protocol, all patients were  
97 decolonized with intra-nasal mupirocine 2 days before surgery (23). Patients received 1.5g of  
98 intravenous cefuroxime at the beginning of the procedure, and then 750mg every two hours  
99 until the end of operation for surgical prophylaxis

100 Patients were informed of the prospective collection of the data and those who declined were  
101 excluded from the study. The local ethics committee (« comité d'éthique du CHU de  
102 Rennes ») approved the study (N°19.53).

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105 **Definitions**

106 Based on previous publications which reported that the vast majority of HAI were due to  
107 hospital acquired bloodstream infection (BSI), hospital acquired pneumonia (HAP) and SSI,  
108 and because other HAI (such as urinary tract infections) have not been associated with an  
109 increased mortality, only BSI, HAP and SSI were included in this study (10-17). We  
110 considered HAI to be those diagnosed more than 48 hours after admission and which were not  
111 incubating on admission, per CDC guidelines (24, 25). BSI was defined as one positive blood  
112 culture, except for common skin contaminants (coagulase negative *Staphylococcus* species,  
113 *Corynebacterium* species, *Propionibacterium acnes* and *Micrococcus* species) where BSI  
114 required two positive blood cultures drawn on separate occasions.

115 The diagnosis of HAP included both ventilated and non-ventilated patients and was based on  
116 clinical signs (fever), radiographic findings (new infiltrate on chest-X-ray or CT scan), a  
117 positive microbiological culture of an endotracheal aspirate ( $\geq 10^6$  colony-forming units/mL)  
118 or a broncho-alveolar lavage ( $\geq 10^4$  colony-forming units/mL) and leukocytosis. Finally, SSI  
119 was defined by fever, clinical or radiographic evidence of wound infection (erythema,  
120 purulent drainage, wound dehiscence, rim-enhancing collections), and micro-organism(s)  
121 identified from the deep soft tissues. Only thoracic wound infections were considered, not  
122 peripheral SSIs such as at the site of vein harvest. Diagnosis of HAI was made by the treating  
123 physician, and independently confirmed by two study physicians who reviewed relevant  
124 imaging, microbiologic data, and medical records.

125 Baseline patient characteristics were collected on admission (age, sex, diagnostic category  
126 [planned versus emergency surgery], admission from another ICU, body mass index, chronic

kidney disease, chronic respiratory failure, cirrhosis, cancer, diabetes, hypertension, stroke, intubation before surgery). Other data were collected during surgery (circulatory arrest for surgery, duration of cardio-pulmonary bypass, transfusion of blood products) and during the hospital stay (number of days at risk for HAI, intubation for more than 48 hours, use of a ventricular assist device, catecholamine use after surgery, post-operative left ventricular dysfunction, stroke, reoperation). Definitions are available in the supplementary data. The number of days at risk for HAI was the number of days in the hospital from the 48<sup>th</sup> hour of stay until discharge or death (for patients without HAI) or until the first HAI occurrence (for patients with HAI). The day of HAI diagnosis was considered as the day of collection of the positive microbiological sample associated with the HAI.

### **Primary and secondary endpoints**

The primary endpoint of the study was the attributable mortality fraction due to HAI after a cardiac operation. HAI attributable mortality fraction is the proportion of death due to HAI, or, in other words, the proportion of all death that might be prevented by eliminating HAI (26). This was calculated by comparing the difference in the number of deaths in patients who developed HAI with the number of deaths in a group of propensity-matched patients who did not develop HAI, (i.e. Attributable mortality = [number of hospital deaths among patients with HAI – number of hospital deaths among matched patient]/ number of hospital deaths in whole cohort). Secondary endpoints were the association between hospital death and microorganisms responsible for HAI or the sites of HAI (i.e. BSI, HAP, SSI).

## Statistical analysis

Statistical analysis was performed with the statistical software R 3.4.3. Incidence and prevalence were expressed with the 95 percent confidence interval (95% CI). Categorical variables were expressed as number (percentage) and continuous variables as median and interquartile range [IQR]. When appropriate, the chi-square test and the Fisher's exact test were used to compare categorical variables. The Man-Whitney U test and Kruskal-Wallis tests were used for continuous variables when applicable. All tests were two-sided, and a P-value less than 0.05 was considered statistically significant.

The probability of developing a HAI was estimated using a multivariable logistic regression model that incorporated variables associated with HAI, while hazard of death was estimated with a multivariable cox regression model. Due to the high number of variables significantly associated either with death or with HAI, only variables with a p-value  $<0.05$  in the univariate analysis were included in the multivariable analysis. Then, to draw unbiased marginal estimates of exposure effect, a propensity-score matched analysis was performed. As potential confounders, we included for propensity-score matching all non-redundant variables independently associated with HAI (event) or death during hospital stay (outcome) with p-value  $\leq 0.05$  in the logistic regression (HAI) or cox-model (death) multivariable analysis.

Using the MatchIt package, a k-nearest neighbor algorithm was used for propensity-score matching with a 1:1 ratio. Each patient with HAI was matched with 1 patient without HAI.

Multivariable competitive risk analysis was performed using the Fine–Gray model for the cumulative incidences of the competing events, namely discharge alive and death during hospital stay (27). The Fine-Gray model measures the association between HAI and outcome (death in Hospital) in which the competing event (discharge alive) actively contributes to modify the risk of the outcome. Therefore subdistribution Hazard Ratio (sdHR)  $>1$  indicates

that those with exposure (HAI) will be seen to have a quicker time to death. Conversely, a  $sdHR < 1$  indicates a longer time before death for those exposed (27). Because HAI developed during survey and not at inclusion, we used a multistate model (28). Therefore, patients with HAI were included twice, first in the group without HAI during the period at risk of HAI, then they were censored from this group and were included in the HAI group only from HAI onset until discharge or death.

The analytic steps can be summarized as follows: first, patients with HAI were matched with similar patients without HAI based on their probability (propensity score calculation) to develop HAI and to die during hospital stay. Then, among patients with HAI and matched patients, we compared the association between HAI and death during hospital stay. Finally, excess of death (difference in the number of dead) in the HAI group was used to estimate HAI attributable mortality fraction in the full cohort.

## RESULTS

### Population

Of 8,969 admissions for cardiac surgery during the study period, 8,893 patients had a length of stay in hospital of 2 days or more and were therefore exposed to the risk of HAI. Of these, 40 patients (0.4%) were excluded due to missing data, leaving a study cohort of 8,853 patients (supplementary Figure 1). Median age was 69 years [61–77] and the most common comorbidity was hypertension, which affected 4,893 patients (55.3%). Predicted mortality based on EUROSCORE II was 2.3%. The majority of operations were elective (87.2%), cardiopulmonary bypass lasted for 74 minutes [55–106] and only 1,589 patients (17.9%) received homologous red-blood cells during their operation. The median length of hospital stay was 10 days [8–14] and 211 patients (2.4%) died during hospital stay (Table 1).

## **Incidence and risk factors for hospital acquired infection**

Of 8,853 patients with a length of stay of 2 days or more, 370 (4.2%) acquired a total of 500 infections during their stay: 110 had one or more BSI (1.2%), 161 had one or more HAP (1.8%) and 173 had one or more SSI (2.0%). The 500 infections occurred over a total of 118,424 days of hospitalization, therefore the HAI incidence density rate was 4.2 HAI per 1,000 patient-days. Factors independently associated with HAI were assessed with a logistic-regression model. Among pre-operative variables, BMI>30 kg/m<sup>2</sup> (Odd Ratio [OR] = 1.55; 95% CI [1.20–2.00] p <0.001), chronic renal failure (OR = 1.66; 95% CI [1.13–2.45] p =0.009), chronic respiratory failure (OR = 1.65; 95% CI [1.17–2.35] p =0.005) and diabetes (OR = 1.43; 95% CI [1.08–1.89] p =0.006) were independently associated with HAI. Five surgical factors were independently associated with HAI: valve replacement (OR = 0.58; 95% CI [0.44–0.77]; p <0.001), combined operations (OR = 1.64; 95% CI [1.15–2.33]; p <0.001) emergency operations (OR = 1.77; 95% CI [1.33–2.33]; p <0.001), CPB length > 100 min (OR = 1.68; 95% CI [1.28–2.19] p <0.001) and platelet transfusion (OR = 1.58; 95% CI [1.09–2.29] p =0.016). Finally, post-operative variables associated with HAI were intubation > 48 hours after cardiac operation (OR = 6.89; 95% CI [4.70–10.09] p <0.001), reoperation (OR = 3.13; 95% CI [2.39–4.11] p <0.001), left ventricular ejection fraction < 50% (OR = 1.35; 95% CI [1.05–1.74] p =0.018) and stroke (OR = 2.22; 95% CI [1.18–4.17] p =0.013) (Table 2).

## **Hazard ratio for death during hospital stay**

Variables associated with death were evaluated using a cox-model regression. Several variables were identified. With cox model regression analysis, HAI was still independently associated with death during hospital stay (HR = 4.39; 95% CI [3.06–6.30]; p <0.001) (Table 3). A sub-group analysis was performed with respect to type of surgery. Among the 5,441

patients with valve surgery, HAI was independently associated with death during hospital stay (sdHR 4.08 [2.78-5.99]  $p < 0.001$ ). Similarly, among the 3,468 patients who underwent coronary artery bypass grafting (CABG), HAI was also independently associated with death during hospital stay (sdHR 4.56 [2.59-8.04]  $p < 0.001$ ). Because SSI was not associated with death in the whole population, a not previously specified analysis was performed in the 3,468 patients who underwent CABG. Of these patients 101 (2.9%) developed a SSI, of whom 6 died (5.9%). Of the 3367 patients without SSI, 53 patients died (1.6%). When a multivariable Fine-Gray analysis was performed, SSI was independently associated with death in Hospital (sdHR=2.94; 95%CI [1.39-6.22];  $p=0.005$ ).

### **Hospital-acquired infection attributable mortality fraction with propensity-score matched analysis**

For propensity score matching, every variable independently associated with HAI or death during hospital stay was included in the analysis. Based on these results, the 370 patients with HAI were matched with 370 patients without HAI (supplementary Figure 2). Baseline characteristics of the 2 groups are reported in Table 1 and were fully balanced, as was predicted mortality with EUROSCORE II ( $p = 0.90$ ). When a cumulative risk analysis with discharge and death as competing variables (Fine and Gray) was performed in this dataset, patients with HAI had a higher risk for death (sdHR = 5.39; 95% CI [3.70-7.86];  $p < 0.001$ ). Among patients with HAI 57 patients died during hospital stay (15.4%), compared with 21 patients without HAI (5.7%,  $p < 0.001$ ) (supplementary Figure 3). Based on these results, the number needed to harm was 10 [7-19] (i.e. there was 1 supplementary death per 10 patients exposed to HAI). Since there were 36 excess deaths in the HAI group, the attributable mortality fraction of HAI in the overall population was 17.1 % [12.3% – 22.8%] (i.e. 17.1%

of the hospital deaths after cardiac operations were related to HAI). Similarly, among patients with HAI, more deaths were observed (57 patients, 15.4%) than were predicted by EUROSCORE II (16 patients, 4.3%) ( $p < 0.001$ ).

#### Outcomes of patients with hospital-acquired infection by microorganism

Of the 370 patients with HAI and 370 propensity-score matched patients, *Pseudomonas aeruginosa* was the only HAI microorganism associated with an increased risk of hospital death after adjustment for site of infection with a Fine-Gray model (sdHR = 2.09; 95% CI [1.23-3.49];  $p = 0.005$ ) (Figures 1 and 2). Microorganisms responsible for HAI are reported by site of HAI in Table 4.

#### Outcomes of patients with hospital-acquired infection by site of infection

Conversely, after adjustment for microorganisms responsible for HAI with Fine-Gray model, bloodstream site of infection (sdHR = 2.08; 95% CI [1.19–3.63]  $p = 0.010$ ) and pneumonia (sdHR = 1.68; 95% CI [1.02–2.77];  $p = 0.04$ ) were independently associated with an increased hazard for death during hospital stay (Figure 1 and 2).

## DISCUSSION

This study demonstrated that while hospital acquired infections were a relatively uncommon complication after cardiac operations, they were responsible for approximately one sixth of hospital deaths. This increased post-operative mortality was observed with both cox regression model, and when comparing patients with HAI to propensity-score matched patients without HAI using a Fine-Gray model. The relatively low rate of HAI observed in this study was in line with previous studies of HAI in a cardiac surgery setting (11-14). This



study confirmed the previously described association between HAI and death (13, 17, 19-21) but is, to our knowledge, the first estimation of HAI-attributable mortality fraction in a large cohort of patients who underwent cardiac operations.

Attributable mortality of ICU-acquired infection has been widely studied in both medical and surgical ICUs (1-9). Although association between ventilator-associated pneumonia (VAP) and death remains controversial in medical patients, other studies have provided evidence of such an association in surgical patients (7, 9). In a large meta-analysis of randomized trials of VAP prevention involving 6,284 patients, Melsen et al. estimated a VAP attributable mortality of 69 % in surgical patients, compared with 0% for medical patients (9). Similar results were found in a large French prospective study including 2,873 mechanically ventilated patients, with an attributable mortality of approximately 10% in surgical patients compared with no attributable mortality in medical patients (7).

Patients undergoing cardiac operations differ notably from patients admitted in other surgical ICUs due to exposure to CPB. Exposure of the patients' blood to the non-endothelialised surface of the circuit results in the widespread activation of the innate immune system that may modify the response to secondary infection (29, 30). Prior studies have demonstrated that patients exposed to extra-corporal circulation are at increased risk of colonization and secondary infection with multidrug resistant bacteria and that these infections are associated with increased mortality (31, 32). Further studies are needed in order to clarify the physiopathology of HAI after CPB.

Among the cardiac surgery patients in this study, both bloodstream infections and pneumonia were associated with increased in-hospital mortality, but there was no association between SSI and mortality. These findings differ from a previous study where Mazeffi et al. reported that SSI and BSI were associated with mortality in cardiac surgery patients with prolonged

ICU stays, whereas pneumonia was not (13). This difference may be explained by differences in the patient population. Mazeffi et al. including only patients with prolonged ICU stays, while this study included all patients who underwent cardiac operations. Others studies supported an increased risk for death in patients with BSI or pneumonia (19, 20) and in patients with SSI (13, 16). As our findings concerning the association between SSI and mortality differ from prior published work, we performed a not pre-specified analysis among patient with CABG operations, who are known to be at higher risk for SSI (16). In this subgroup of patients, SSI was associated with increased in-hospital mortality, suggesting that a difference in patient populations may account for this finding.

Among micro-organisms responsible for HAI, *Pseudomonas aeruginosa* is one of the most common gram-negative pathogens and has been responsible for well-documented ICU epidemics (33-36). Compared with other microorganisms, including non-fermenting gram-negative bacilli, *Pseudomonas aeruginosa* has been associated with an increased morbidity and mortality in our study, as in previous publications (2, 35, 36). Assessing excess mortality and length of stay in ICU in patients with BSI or pneumonia, Lambert et al. found that infection due to *Pseudomonas aeruginosa* reduced hazard ratio for ICU discharge. The authors concluded that this microorganism carried the highest burden of health-care-associated infections because of its high prevalence and pathogenicity (2). We observed similar results in our study, as only *Pseudomonas aeruginosa* infections were associated with death among patients with HAI and propensity-score match patients. Other authors report similar result, with a higher attributable mortality for BSI due to Gram-negative bacteria than to other microorganisms (19). However, they did not separately analyze the influence of *Pseudomonas aeruginosa* versus other Gram-negative bacteria.

The main strengths of our study are the large patient population and the use of propensity-matching to reduce the impact of potential confounders (6, 19). While the nature of hospital-acquired infections requires an observational study design, the propensity score matching in this study was highly effective and measured characteristics of patients with HAI and propensity-score matched patients were well balanced. In addition, we were able to account for the competing event nature of the main outcome.

Our study has also several limitations. First, the time dependency of mortality on HAI was not extensively studied as we could not obtain patient-related variables specific to the day of HAI (for example sequential organ failure assessment score or use of epinephrine on the day of HAI). Such data would have reduced time-dependent bias. Moreover, relative risk of HAI could differ during hospital stay with a higher risk of HAI in the ICU than in other wards. Although a multistate model took into account the length of stay before HAI occurrence, we could not distinguish length of stay in the ICU from length of stay in another ward. Therefore, although we performed a multivariable analysis and case-control matching to reduce time dependency bias time dependency may still be considered a potential confounder. Second, we did not have data regarding antimicrobial susceptibility or the appropriateness of antimicrobial agents used for HAI treatment. However, prior studies have reported that the additional effect of antimicrobial resistance patterns on attributable mortality is comparatively low (2). Third, due to missing data, we did not control for some other residual confounders such as glucose control, steroid administration, immunosuppression, or obesity/malnutrition. Fourth, the diagnosis of HAI was made by the treating physician. Although HAI diagnosis was independently confirmed by two study physicians, this remains a limitation. This is particularly true for the diagnosis of pneumonia, which was made using a set of clinical criteria described above, though less of an issue for SSI and BSI where diagnosis relied on

documented culture data. Finally, this was a retrospective single center study, limiting its external generalizability.

## CONCLUSION

In this large prospective observational study, HAI after cardiac surgery was associated with an increased risk for death especially for BSI and pneumonia or when *Pseudomonas aeruginosa* was involved. The fraction of mortality attributable to HAI was 17.1 %. This result can be used as a benchmark in order to evaluate strategies that aim to reduce HAI incidence and attributable mortality fraction in cardiac surgery setting.

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## Declarations of interest

None.

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## Figure legends

### Figure 1

Subdistribution Hazard ratios (sdHR) for hospital death among 370 cardiac surgery patients with hospital acquired infection (HAI) and 370 propensity score-matched patients without HAI. Competitive risk analysis was performed with a Fine-Gray method with discharge and death being competing outcomes. Diamonds correspond to the estimated sdHR and bars delimit 95% confidence intervals. For subgroup analysis, patients exposed to a risk (for example pneumonia) were compared to all other patients in the cohort without exposure (all patients without pneumonia among those with a HAI and the 370 matched patients).

\* Subgroup analysis by site of infection was adjusted for micro-organism

\*\* Subgroup analysis by microorganism was adjusted for site of infection

Figure 2: Graphical abstract: Mortality attributable to hospital-acquired infections (HAI) after cardiac surgery and subdistribution Hazard Ratios (sdHR) for hospital death for the following sub groups: Pneumonia, Bacteremia and *Pseudomonas Aeruginosa* infections

Video 1: Mortality attributable to hospital-acquired infections after cardiac surgery: Nicolas Nessler presents the findings and implications of the study.

Table 1: Baseline characteristics and outcomes of study patients.

Variables	All patients n = 8854		Patients with HAI n = 370		Propensity-score matched patients n = 370		p-value*	Standardized Difference*
Age, year [IQR]	69	[61-77]	68	[59-75]	68	[59-75]	0.98	0.060
Body mass index, [IQR]	26.3	[23.7-29.3]	26.8	[24.4-30.3]	26.8	[23.6-30.5]	0.54	0.013
Male – no. (%)	6491	(73.3)	285	(77.0)	293	(79.2)	0.48	0.021
Euroscore II predicted mortality, – % mean (SD)	2.4	(3.4)	4.3	(6.4)	4.2	(6.3)	0.90	
<i>Comorbidities</i>								
Chronic kidney failure – no. (%)	428	(4.8)	40	(10.9)	43	(11.6)	0.82	0.008
Chronic respiratory failure – no. (%)	663	(7.5)	43	(11.6)	37	(10.0)	0.55	0.016
Cirrhosis – no. (%)	53	(0.6)	2	(0.5)	0	(0.0)	0.48	0.005
Cancer – no. (%)	662	(7.5)	32	(8.6)	25	(6.7)	0.41	0.002
Diabetes – no. (%)	1411	(15.9)	83	(22.4)	94	(25.4)	0.39	0.030
Hypertension – no. (%)	4893	(55.3)	200	(54.1)	219	(59.2)	0.18	
Stroke – no. (%)	188	(2.1)	8	(2.2)	13	(3.5)	0.37	
<i>Pre-surgery</i>								
Intubation – no. (%)	21	(0.3)	4	(1.1)	2	(5.4)	0.68	
Admission from another ICU – no. (%)	38	(0.5)	4	(1.1)	4	(1.1)	1	0.001
<i>Surgery</i>								
Valve – no. (%)	5441	(61.5)	189	(51.1)	202	(54.6)	0.42	0.035
Coronary artery by-pass – no. (%)	3468	(39.2)	160	(43.2)	161	(43.5)	1	0.002
Combined – no. (%)	910	(10.3)	57	(15.4)	58	(15.7)	0.94	0.005
Other – no. (%)	858	(9.7)	78	(21.1)	65	(17.6)	0.33	
Emergency surgery – no. (%)	1136	(12.8)	113	(30.5)	121	(32.7)	0.58	0.022
Circulatory arrest – no. (%)	370	(4.2)	29	(7.8)	41	(11.1)	0.17	
Length of CPB, minutes [IQR]	74	[55-106]	100	[64-145]	105	[69-145]	0.54	0.043
Red-blood cell transfusion – no. (%)	1589	(17.9)	110	(29.7)	114	(30.8)	0.81	0.011
Platelet transfusion – no. (%)	547	(6.2)	65	(17.6)	71	(19.2)	0.64	0.016
<i>Post-operative events</i>								
Intubation for > 48 hours – no. (%)	178	(2.0)	58	(15.7)	47	(12.7)	0.29	0.030
Stroke – no. (%)	155	(1.8)	18	(4.8)	15	(4.1)	0.86	0.005
Left ventricular ejection – % [IQR]	61	[55-65]	60	[45-65]	60	[45-65]	0.26	0.002
Reoperation – no. (%)	807	(9.1)	109	(29.5)	112	(30.3)	0.87	0.008
Ventricular assist device – no. (%)	466	(5.3)	60	(16.2)	61	(16.0)	1	0.003
<i>Outcome</i>								
Length of stay in hospital, days [IQR]	10	[8-14]	24	[11-40]	13	[9-22]	<0.001	
Death during hospital stays – no. (%)	211	(2.4)	57	(15.4)	21	(5.7)	<0.001	
Death at day 90 – no. (%)	261	(2.9)	74	(20.0)	28	(7.6)	<0.001	

Note. HAI: Hospital-acquired infection. IQR: Inter-quartile ranges. SD: Standardized derivation. ICU : intensive care unit. CPB : cardio-pulmonary bypass. \* For comparison between patients with HAI and matched patients.

Table 2: Risk factors for hospital-acquired infection.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, per supplementary year	0.99	0.98-1.00	0.009	1.00	0.99-1.01	0.79
Body mass index > 30 kg/m <sup>2</sup>	1.42	1.12-1.80	0.033	1.55	1.20-2.00	<0.001
Male	1.23	0.96-1.57	0.10			
Chronic kidney failure	2.53	1.79-3.57	<0.001	1.66	1.13-2.45	0.009
Chronic respiratory failure	1.71	1.24-2.36	0.001	1.65	1.17-2.35	0.005
Cirrhosis	0.88	0.22-3.71	0.85			
Cancer	1.67	1.20-2.32	0.002	1.20	0.81-1.77	0.37
Diabetes	1.56	1.21-2.00	0.005	1.43	1.08-1.89	0.006
Hypertension	0.95	0.77-1.17	0.63			
Stroke history	1.02	0.50-2.09	0.96			
Intubation before surgery	5.44	1.82-16.26	0.002	1.89	0.56-6.34	0.31
Admission from another ICU	2.71	0.96-7.69	0.060			
Valve	0.64	0.52-0.79	<0.001	0.58	0.44-0.77	<0.001
Coronary artery by-pass	1.19	0.97-1.47	0.10			
Combined	1.59	1.15-2.14	0.002	1.64	1.15-2.33	0.006
Other	2.64	2.04-3.43	<0.001	0.95	0.65-1.39	0.79
Emergency surgery	3.20	2.55-4.04	<0.001	1.77	1.33-2.36	<0.001
Circulatory arrest for surgery	2.05	1.39-3.02	<0.001	0.68	0.41-1.13	0.14
Length of CPB >100 minutes	2.67	2.17-3.30	<0.001	1.68	1.28-2.19	<0.001
Red-blood cell transfusion during surgery	2.00	1.59-2.52	<0.001	1.06	0.80-1.40	0.71
Platelet transfusion during surgery	3.54	2.67-4.70	<0.001	1.58	1.09-2.29	0.016
Intubation for > 48 hours after surgery	13.41	9.59-18.74	<0.001	6.89	4.70-10.09	<0.001
Stroke after surgery	4.87	2.86-8.30	<0.001	2.22	1.18-4.17	0.013
Left ventricular ejection < 50% after surgery	2.17	1.75-2.71	<0.001	1.35	1.05-1.74	0.018
Ventricular assist device after surgery	3.85	2.87-5.17	<0.001	1.34	0.93-1.95	0.12
Reoperation during hospitalization	4.66	3.68-5.90	<0.001	3.13	2.39-4.11	<0.001
Length of exposure to the risk, per supplementary days	1.01	1.00-1.01	0.002	1.00	0.99-1.01	0.95

Note. ICU : intensive care unit. CPB : cardio-pulmonary by pass.

Table 3 : Hazard ratio for death during hospital stay.

	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age. per supplementary year	1.02	1-1.03	0.016	1.05	1.03-1.07	<0.001
Body mass index > 30 kg/m <sup>2</sup>	0.82	0.57-1.18	0.289			
Male	0.57	0.43-0.76	<0.001	0.57	0.42-0.77	<0.001
Chronic kidney failure	3.12	2.08-4.68	<0.001	1.68	1.1-2.57	0.016
Chronic respiratory failure	1.76	1.16-2.68	0.008	1.59	1.04-2.44	0.034
Cirrhosis	5.29	2.35-11.91	<0.001	4.72	2.02-11.03	<0.001
Cancer	1.69	1.1-2.59	0.016	1.56	1.01-2.41	0.043
Diabetes	1.4	1-1.97	0.052			
Hypertension	0.98	0.74-1.29	0.89			
Stroke history	1.93	0.95-3.92	0.068			
Intubation before surgery	6.86	2.2-21.46	0.001	1.1	0.33-3.63	0.88
Admission from another ICU	7.5	3.33-16.91	<0.001	4.05	1.7-9.64	0.002
Valve	0.99	0.75-1.31	0.943			
Coronary artery by-pass	0.64	0.47-0.87	0.004	0.77	0.49-1.2	0.25
Combined	1.66	1.14-2.43	0.008	1.46	0.84-2.54	0.18
Other	3.31	2.41-4.53	<0.001	1.35	0.9-2.02	0.15
Emergency surgery	4.41	3.32-5.86	<0.001	2.1	1.46-3.02	<0.001
Circulatory arrest for surgery	2.44	1.52-3.92	<0.001	0.7	0.4-1.22	0.21
Length of CPB >100 minutes	3.8	2.87-5.04	<0.001	1.91	1.33-2.72	<0.001
Red-blood cell transfusion during surgery	4.19	3.18-5.53	<0.001	1.47	1.05-2.04	0.023
Platelet transfusion during surgery	5.07	3.68-7	<0.001	1.36	0.92-2.03	0.12
Intubation for > 48 hours after surgery	8.76	5.91-12.99	<0.001	1.61	1.01-2.55	0.043
Stroke after surgery	6.88	4-11.84	<0.001	2.57	1.44-4.59	0.001
Left ventricular ejection < 50% after surgery	2.57	1.94-3.41	<0.001	1.54	1.12-2.12	0.009
Ventricular assist device after surgery	7.56	5.57-10.28	<0.001	2.9	1.99-4.23	<0.001
Reoperation during hospitalization	3.64	2.66-4.98	<0.001	1.45	1.01-2.08	0.045
<i>Hospital-acquired infection</i>						
Any	9.87	7.26-13.41	<0.001	4.39	3.06-6.3	<0.001
Bloodstream infection	13.44	8.90-20.29	<0.001	3.98	2.46-6.44	<0.001
Pneumonia	14.83	10.42-21.11	<0.001	4.54	3.00-6.87	<0.001
Surgical-site infection	2.69	1.43-5.08	<0.001	1.59	0.82-3.09	0.17

Note. ICU : intensive care unit. CPB : cardio-pulmonary by pass.

Table 4. Microorganisms responsible for Hospital-acquired infection.

Microorganisms	All isolates		Bloodstream infection		Pneumonia		Surgical site infection	
	n	(%)	n	(%)	n	(%)	n	(%)
<i>Staphylococcus-aureus</i>	143	(23.7)	72	(38.5)	24	(9.9)	47	(27.0)
Coagulase-negatives <i>Staphylococci</i>	114	(18.9)	38	(20.3)	6	(2.5)	70	(40.2)
<i>Enterococcus sp.</i>	18	(3.0)	9	(4.8)	3	(1.2)	6	(3.4)
<i>Streptococcus sp.</i>	30	(5.0)	8	(4.3)	19	(7.8)	3	(1.7)
<i>Pseudomonas aeruginosa</i>	95	(15.7)	23	(12.3)	66	(27.1)	6	(3.4)
<i>Enterobacteriaceae</i>	114	(18.9)	27	(14.4)	58	(23.8)	29	(16.7)
<i>Anaerobes</i>	10	(1.7)	5	(2.7)	0	(0)	5	(2.9)
<i>Others</i> Gram-negative bacilli *	47	(7.8)	1	(0.5)	45	(18.5)	1	(0.6)
<i>Candida sp.</i>	3	(0.5)	2	(1.1)	0	(0)	1	(0.6)
<i>Others**</i>	30	(5.0)	2	(1.1)	22	(9.1)	6	(3.4)
Total	604	(100)	187	(100)	243	(100)	174	(100)

\* Included *Haemophilus sp.*, *Pasteurella sp.* and *Stenotrophomonas sp.*

\*\* Included *Moraxella sp.*, *Neisseria sp.* and *Corynebacterium sp.*



**Mortality attributable to hospital-acquired infections after cardiac surgery**

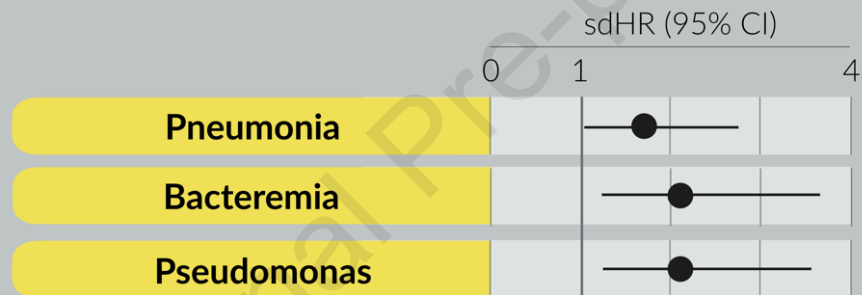
8,853 patients

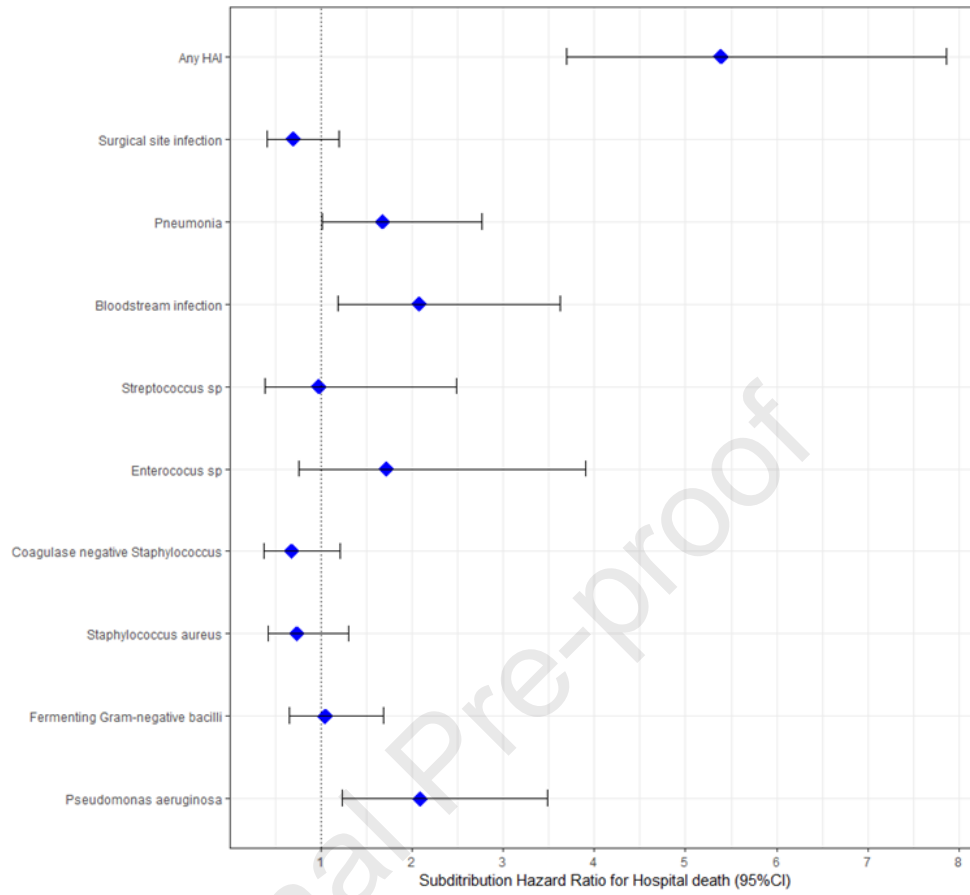


Cardiac surgery



2012-2019

**Postoperative infections**  
4 %**Attributable mortality**  
17 %**In hospital mortality in patients with hospital-acquired****Low incidence but major impact on postoperative mortality**



**Mortality attributable to hospital-acquired infections after cardiac surgery**

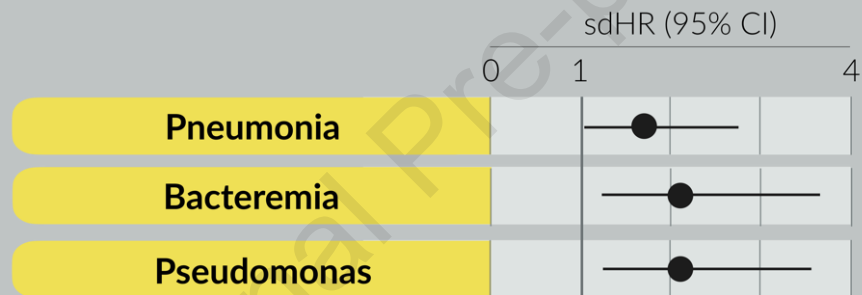
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