Methicillin-Resistant Staphylococcus Species in a cardiac surgical intensive care unit

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Abstract

Objective. Multi-drug resistant bacterial infections, in particular when Methicillin-Resistant Staphylococcus Aureus (MRSA) is involved, have become a relevant problem in both general and specialized intensive care units. The aim of this study was to identify the epidemiology of MRSA infections in a Cardiac Surgical Intensive Care Unit, to assess their impact on mortality and to identify predictors of MRSA infection and mortality in this population.

Design and settings. A 7-year observational study in a cardiac surgery teaching center.

Participants. Eight thousand, one hundred and sixty-two microbiological samples were obtained from 7,313 patients who underwent cardiac surgery in the study period.

Interventions. None.

Variables of interest and main results. Twenty-eight patients (0.38%) had

MRSA infection. The most frequent site of MRSA isolation was from bronchoalveolar samples. Hospital mortality was 50% in patients with MRSA infection and 2% in patients without MRSA infection ($p<0.001$).

Few preoperative independent predictors of MRSA infection and hospital mortality were found at multivariate analysis. Outcomes were found to be most influenced by perioperative variables. MRSA infection was the strongest predictor of mortality, with an odds ratio of 20.5 (95% CI 4.143-101.626).

Conclusions. Methicillin-resistant Staphylococcus aureus infections following cardiac surgery still have a strong impact on the patients' outcome. More efforts should be directed toward the development of new risk analysis models that might implement health care practices and might become precious instruments for infection prevention and control.

Key words: Methicillin-Resistant Staphylococcus Aureus, infections, cardiac surgery, mortality, intensive care, cardiac anaesthesia

Introduction

Despite considerable improvements in surgical techniques and antibiotic therapies in the last decades, Healthcare Associated Infections (HAI) in surgical patients admitted to Intensive Care Units (ICU) continue to be among the most severe complications, especially after cardiac surgery. (1,2)

Infections after cardiac operations are associated with poor outcomes, including elevated readmission rates, prolonged hospital stay, higher rate of surgical revisions, administration of antibiotics, and adoption of resources that comply with higher health care costs and mortality. (1,2) Among the various species of pathogens involved, *Staphylococcus aureus* strongly impacts on the outcomes of these patients. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have become a relevant problem in cardiac surgery because of their multidrug-resistant profile, virulence and disease spectrum.

All over the world, ICUs may a have a role in the selection of resistant

microbiological strains. Therefore, a strict surveillance system, to prevent the spread of these strains, is a major public health challenge and often requires several institutional efforts. (3-7)

The aim of this study was to identify the epidemiology of MRSA strains among the microbiologic isolates in a Cardiac Surgical Intensive Care Unit over a 7-year period, to assess its impact on mortality and to identify predictors of MRSA infection and mortality in this population. These results will be commented in the light of similar data reported by our study group on a similar population of cardiac surgery patients in the past. (1)

Patients and methods

The study was conducted in compliance with the Declaration of Helsinki and had the approval of the local ethical committee. We analyzed data of patients who underwent cardiac surgery at San Raffaele Scientific Institute over a seven-year period. Our teaching hospital has 3 cardiac surgery operating rooms, and a 14 bed dedicated ICU. All patients underwent cardiac surgery under general anesthesia and were transferred, intubated, to the ICU.

All patients received standard postoperative intravenous therapy, including hydration, antacids and diuretics, together with inotropes and devices, if needed.

Similarly, intravenous antibiotic prophylaxis was performed shortly after the induction of general anesthesia and maintained for the first 48 hours postoperatively: 2 g of cefazolin was used as an induction bolus (in patients with known allergy to beta-lactams, either vancomycin 1 g or clindamycin 600 mg were used), and 1 g 3 times a day was the standard maintenance dose (or vancomycin 500 mg 4 times a day).

Infection was suspected if a patient developed fever (body temperature T>38 C°), an increase in white blood cell count, changes in the chest X-ray consistent with pneumonia, worsening of respiratory function not due to cardiogenic pulmonary oedema or a new increase in C reactive protein.

When an infection was suspected, 3 sets of blood cultures, deep tracheal aspirate or bronchoalveolar lavage, and urine samples were sent to the laboratory for microbiological examination.

In addition, if an intravascular device infection was suspected, the device was changed or removed and the tip was sent for microbiological investigation.

If considered appropriate, a wide spectrum antibiotic was initiated before completion of microbiological tests.

Generic prophylactic measures were routinely applied, such as hand washing and use of gloves. No specific prophylactic measures were routinely adopted (i.e. preoperative screening of Staphylococcus species carriers, screening of medical staff, application of topical chlorhexidine).

Hemodynamic monitoring was performed for each patient according to clinical needs. Acute kidney damage was diagnosed in the presence of an increase in serum creatinine value of 50% or a decrease in glomerular filtration rate of 25%, compared to preoperative data. (8) Creatinine clearance was estimated according to the Cockroft-Gault equation (9) and the age, creatinine, and ejection fraction (ACEF) score was also calculated. (10)

Patients' information and clinical preoperative, intraoperative, and postoperative data were collected. Categorical variables are reported as numbers (percentage), whereas continuous variables are expressed as mean ± standard deviation or as median (interquartile range), according to the Kolmogorov-Smirnov test.
Fisher's test was used to calculate p-values between 2 groups for categorical variables, whereas Wilcoxon test was used for continuous variables.
Multivariate analysis was performed using a stepwise logistic regression. The set of covariates was based on the univariate logistic model: all the variables with a p-value < 0.2 were included in the multivariate model. A further dicotomous variable, the "presence of at least 3 comorbidities", was created and tested in the multivariate models. All statistical analyses were performed with SAS software (release 9.2 by SAS Institute Inc.

Cary, NC, USA).

Results

Eight thousand, one hundred and sixty two microbiological samples were analyzed for suspicion of infection in the 7,313 patients who underwent cardiac surgery in the study period. The majority of samples (72%) had no microorganism isolated. Staphylococcus spp was the most frequently isolated germ in our ICU during the study period, with 876 positive samples out of 8,162. The 876 samples belonged to 339 patients. Staphylococcus aureus spp were isolated in 338 samples from 124 patients. Infection with MRSA was recorded in 47 microbiological samples from 28 patients (0.38%). The most frequently isolated germs are summarized in table 1.

The mean age of the overall study population was 60 ± 13.7 years, and 4,696 (64%) were male. One hundred-sixty three patients (2.2%) died. The number of patients with MRSA infection, stratified according to years, was always below 1% and is reported in figure 1. Mortality in patients with MRSA infection over the years 2003-2009 was 80% (4 out of 5 patients), 67% (2 out of 3 patients), 50% (1 out of 2 patient), 37% (4 out of 11 patients), 0% (0 out of 1 patient), 40% (2 out of 5 patients), and 100% (1 patient), respectively.

Baseline, intraoperative and postoperative data of patients with MRSA infection compared to patients without MRSA infection are reported in table 2. Mortality was 50% in patients with MRSA infection, and 2% in patients without MRSA infection ($p<0.001$). Baseline, intraoperative and postoperative data of patients who survived, compared to patients who died during hospitalization, is shown in table 3.

The site of MRSA isolation is shown in detail in table 4, together with MR not-Aureus Staphylococci. The most frequent site of MRSA isolation was from bronchoalveolar secretions (21 cases). On the contrary, not-Aureus MR Staphylococci were most frequently found in blood samples (100 cases). Multivariate analysis of preoperative and intraoperative factors which were significantly associated with MRSA positivity is shown in

table 5.

Table 6 displays the results of multivariate analysis on preoperative and intraoperative factors significantly associated with hospital mortality. Notably, MRSA infection was the strongest predictor of mortality with an odds ratio of 20.5 (95% CI 4.143-101.626).

Discussion

This study analyzed all the patients who underwent cardiac surgery at our institution over a six-year period, focusing on the development of MRSA infections during the cardiac Intensive Care Unit stay. These data are to be compared with those from our previous study conducted between 1997 and 2003 in the same center and enrolling similar patients. First of all, MRSA was observed with a prevalence rate below 1% in the whole study period, compared to the 2% of the pre-existing study. Furthermore, a strong association between MRSA isolation and in-hospital mortality (OR 8.5, 95% CI 4.9-14.7) was observed in 1997-2003 patients. (1) This observation is further reinforced by the consideration that our center has a very low perioperative mortality rate, as recently highlighted. (11) Our study confirmed that infection with MRSA is an independent predictor of mortality (OR 20.5, 95% CI 4.143-101.626) but notably the incidence of MRSA infection recorded is lower compared to the previous population (28 patients).

The issue of MRSA infections in the ICU is greatly discussed in the literature. An observational cohort study, dated 2010, and including 4,949 patients with *Staphylococcus aureus* infection, was conducted to evaluate the clinical impact of methicillin resistance on outcome of patients and concluded that *S. aureus* infections did not adversely affect the outcome. (12) It is presumed that infections caused by MRSA result in higher mortality, longer hospitalization, and greater costs than infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). However, the impact of MRSA on mortality is not easy to determine. The outcomes of infections indeed might depend on individual variables such as underlying medical conditions, treatments administered before surgery, and inappropriate antibiotics use to eradicate postoperative

infections, resulting in increased bacterial resistance.

Our study included patients who received preoperative antibiotic prophylaxis according to the protocol adopted by the center, also in line with the latest reports that confirm that administration of antibiotic prophylaxis in cardiac surgery might reduce the development of both superficial skin and wound infections. (13) In 2013, a systematic literature review and meta-analysis (14) of factors associated with MRSA colonization at time of hospitalization or intensive care unit admission was conducted, including articles from 1966 to 2012, in order to underline how the definition of high risk can differ among hospitals and state laws. Many hospitals screen for MRSA colonization on admission as a key infection prevention strategy. An alternative to universal screening is to test for MRSA among populations at high risk for colonization, but such an approach can be hard on resources and may pose practical challenges. However, it is common agreement that active MRSA surveillance, combined with implementation of barrier precautions, with or without decolonization protocols, has been associated with reduced MRSA transmission in investigations conducted in high prevalence settings. (14) A clear representation of MRSA trend in each centre is surely pivotal to refine the growing practice of MRSA surveillance programs, especially in a cardiac ICU where the critically ill patient's condition is the *humus* for growing risk factors that might be strictly controlled.

We also performed a multivariate analysis in order to identify factors associated with MRSA infection and in-hospital mortality. Despite some differences in the results between the two populations, MRSA infection was confirmed to be an independent predictor of mortality in the 2003-2009 population also.

This observation suggests that, although MRSA infection rate is decreasing, the occurrence of such a complication is still not easy to handle, therefore strong efforts should be made to prevent it. An interesting finding was also the fact that the patients undergoing diuretic therapy before surgery presented a higher risk for MRSA infection. This is not a surprising result, even though the scientific evidence in this field is still limited. Furosemide indeed was already shown to have

immunosuppressive effects on peripheral blood mononuclear cells which are similar to equimolar concentrations, hence, equivalent doses of hydrocortisone. (15)

Another interesting element to comment on is the evaluation of the most typical site of MRSA isolation that remained bronchial secretions for both studies (32 isolations for the previous study conducted in 1997-2003 and 21 for the second one during 2003-2009).

Finally, we also observed a non- negligible rate of fungal infections, especially by Candida spp. Although the prevalence of fungal infections and their impact on survival are beyond the scope of this study, this observation may suggest watchful monitoring in the future.

Based on our data, it is reasonable to conclude that a few elements at baseline may help to stratify which patients are at increased risk of MRSA infection and hospital mortality.

A perception exists that longer ICU stay is directly related to in-hospital mortality, but this supposition is not fully validated in cardiac surgery patients. An effort to characterize postoperative length of ICU stay and to match it with demographic data, preoperative comorbidities, and postoperative complications has been done by a team of anesthesiologists between 2004 and 2012. They collected data of patients that underwent cardiac surgery and demonstrated that, for this cohort of patients, it remained unclear how much the likelihood for mortality increased after each postoperative day in the ICU or hospital. (16)

Our study has some limitations. First, it included patients from a single center and therefore the results cannot be applied to all ICUs, because of the differences in strategies adopted in the prevention and in the control of MRSA infections among ICUs and cardiac ICUs as well as in the different surveillance protocols existing in the various centers. On the other hand, this study represents a valid frame for the evolution of MRSA trend in our center and specifically in our cardiac ICU, defining a continuous state of MRSA infections in the last 2 decades. Another limitation of this study is the lack of a surveillance protocol for isolation of pathogens and decolonization of patients admitted to the ICU. Indeed,

a recent paper gives a landmark for what concerns decolonization to prevent ICU infections. Specifically, both targeted and universal decolonization of patients were adopted in a cluster-randomized trial, and universal decolonization significantly reduced the rate of all bloodstream infections in ICU practice than either targeted decolonization or screening and isolation. (6)

CONCLUSION

MRSA infections in our experience are less common than in the past, yet they still have a strong impact on the patients' outcome. Therefore, efforts should be directed toward the development of new risk analysis models that might implement health care practices and might become precious instruments for infection prevention and control.

References

1. Zangrillo A, Landoni G, Fumagalli L, Bove T, Bellotti F, Sottocorna O et al. Methicillin- Resistant Staphylococcus Species in a Cardiac surgical Intensive Care Unit: a 5- Year Experience. J Cardiothorac Vasc Anesth 2006 Feb;20(1):31-7.
2. European Centre for Prevention and Control. Surveillance Report: Surveillance of surgical site infections in Europe 2010-2011 [online]. 2013 Oct [cited 2014 September 28]; Available from: URL:http://www.ecdc.europa.eu/en/publications/Publications/SSI-in-europe-2010-2011.pdf.
3. Gorlitzer M, Wagner F, Pfeiffer S, Folkmann S, Meinhart J, Fischlein T, et al. Prevention of sternal wound complications after sternotomy: results of a large prospective randomized multicentral trial. Interact Cardiovasc Thorac Surg 2013 Sep;17(3):515-22.
4. Schweizer M, Perenchevic E, McDanel J, Carson J, Formanek M, Hafner J, et al. Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease Gram positive surgical site infections after cardiac or orthopedic surgery: systematic review and meta- analysis. BMJ 2013 Jun 13;346:f2743.
5. Healy DG, Duignan E, Tolan M, Young VK , O'Connell B , McGovern E .

Should cardiac surgery be delayed among carriers of methicillin-resistant Staphylococcus aureus to reduce methicillin- resistant Staphylococcus aureus- related morbidity by preoperative decolonization? Eur J Cardiothorac Surg 2011 Jan;39(1):68-74.

6. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus Universal Decolonization to Prevent ICU Infection. N Engl J Med 2013 Jun 13;368(24):2255-65.
7. Derde LP, Cooper BS, Goossens H, Malhotra-Kumar S , Willems RJ , Gniadkowski M , et al. Intervention to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomized trial. Lancet Infect Dis 2014 Jan;14(1):31-9.
8. Bellomo R , Ronco C , Kellum JA , Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute Dialysis Quality Initiative workgroup . Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004 Aug;8(4):R204-12.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976:16 (1):31-41.
10. 10. Ranucci M, Castelvecchio S, Conte M, Megliola G , Speziale G , Fiore F , et al. The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery. J Thorac Cardiovasc Surg 2011 Sep;142(3):581-6.
11. Landoni G, Pasin L, Monti G, Cabrini L, Beretta L, Zangrillo A. Towards zero perioperative mortality. Heart, Lung and Vessels 2013;5(3): 133-6.
12. Kang CI 1, Song JH , Chung DR , Peck KR , Ko KS , Yeom JS , et al. Clinical impact of methicillin resistance on outcome of patients with Staphylococcus aureus infection. A stratified analysis according to underlying diseases and sites of infection in a large prospective cohort. J Infect 2010 Oct;61(4):299-306.
13. Finkelstein R , Rabino G , Mashiach T , Bar-El Y , Adler Z , Kertzman V , et al. Effect of preoperative Antibiotic Prophylaxis on Surgical Site Infections Complicating Cardiac Surgery. Infect Control Hosp Epidemiol 2014 Jan;35(1):69-74.

14. McKinnell JA,Miller LG, Eels SJ, Cui E, Huang SS. A systematic Literature Review and Meta- Analysis of factors Associated with Methicillin- Resistant Staphylococcus aureus Colonization at Time of Hospital or Intensive Care Unit Admission. Infect Control Hosp Epidemiol 2013 Oct;34(10):1077-86.
15. Yuengsrigul A, Chin TW, Nussbaum E. Immunosuppressive and cytotoxic effects of furosemide on human peripheral blood mononuclear cells. Ann Allergy Asthma Immunol 1999 Dec;83(6 Pt 1):559-66.
16. Mazzeffi M, Zivot J, Buchman T, Halkos M . In-hospital Mortality After Cardiac Surgery: Patient Characteristics, timing, and Association with Postoperative Lenght of Intensive Care Unit and Hospital Stay. Ann Thorac Surg 2014 Apr;97(4):1220-5.
17. Wolman RL, Nussmeier NA, Aggarwal A, Kanchuger MS, Roach GW, Newman MF, et al. Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. Multicenter Study of Perioperative Ischemia Research Group (McSPI) and the Ischemia Research Education Foundation (IREF) Investigators. Stroke 1999 Mar;30(3):514-22.

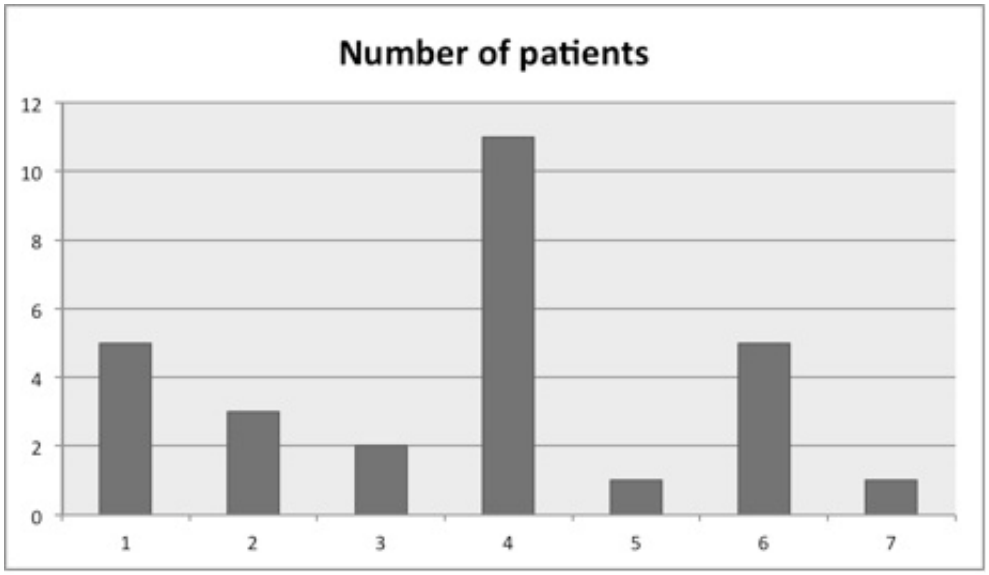

Figure 1. Patients with Methicillin-resistant Staphylococcus Aureus (MRSA) infection per year.

Table 1. The most frequently isolated germs in our Intensive Care Unit (ICU) in the 6-year study period.

Microorganism	**Frequency (percentage)**

Staphylococcus spp	876 (38.4)
> Staphylococcus aureus	338 (14.8%)
> Staphylococcus aureus MR	256 (11.2%)
> Staphylococcus non aureus spp	538 (23.6%)
> Staphylococcus non aureus MR spp	489 (21.4%)
Candida spp	300 (13)
Pseudomonas spp	272 (11.9)
Escherichia spp	134 (5.9)
Enterobacter spp	120 (5.3)
Serratia spp	105 (4.6)
Klebsiella spp	91 (4)
Enterococcus spp	74 (3.2)
Corynebacterium spp	50 (2.2)
Stenotrophomonas spp	47 (2)
Citrobacter spp	33 (1.4)
Proteus spp	33 (1.4)
Haemophilus spp	20 (0.9)
Streptococcus spp	20 (0.9)
Aspergillus spp	18 (0.8)
Acinetobacter spp	14 (0.6)
Morganella spp	14 (0.6)

Table 2. Baseline, intraoperative, and postoperative data of patients with and without Methicillin-resistant Staphylococcus Aureus (MRSA) infection. Continuous data are presented as media ± standard deviation, and categorical variables as number and percentage.

Variable	NO MRSA (N=7285)	MRSA (N=28)	P-Value
Male gender, n	4678 (64%)	18 (64%)	0.9
Age, years	60 ± 13.7	68 ± 12.7	0.007
Height, cm	169 ± 9.2	169 ± 9.2	0.7
Weight, kg	72 ± 13.7	73 ± 19.2	0.7
BMI	25.3 ± 4	25.8 ± 6.3	0.9
Comorbidity			
> Active smoking, n	863 (12%)	3 (11%)	0.9
> COPD, n	1086 (15%)	16 (57%)	< 0.001
> Ejection fraction, %	55.6 ± 10.2	48.7 ± 12.8	0.009
> Ejection fraction <= 40%, n	773 (12%)	8 (36%)	0.003
> Vasculopathy, n	1095 (15%)	9 (32%)	0.018
> Arterial hypertension, n	2697 (37%)	9 (32%)	0.6
> Diabetes, n	722 (9.9%)	5 (18%)	0.2
> Angina, n	499 (6.9%)	2 (7.1%)	0.9
> Acute myocardial infarction, n	675 (9.3%)	2 (7.1%)	0.8
> Euroscore standard	4 (3 – 6)	7 (5 – 9)	0.001
> ACEF mortality risk	1.9 (1.4 – 2.4)	2.5 (2 – 7.86)	0.0012
> Creatinine clearance, ml/h	78.7 (60.4 – 101.1)	55.5 (38.8 – 71.9)	0.0014
> Stroke or transient ischemic attack, n	402 (5.5%)	2 (7.1%)	0.9

> Active bacterial endocarditis, n	137 (1.9%)	1 (3.6%)	0.9
> Creatinine, mg/dl	0.98 ± 0.58	1.68 ± 1.48	0.001
NYHA			0.006
> I, n	984 (20%)	1 (5%)	
> II, n	2518 (51%)	7 (37%)	
> III, n	1322 (27%)	9 (47%)	
> IV, n	79 (2%)	2 (11%)	
Preoperative IABP, n	189 (2.6%)	3 (11%)	0.036
Timing of surgery			< 0.001
> Emergency, n	79 (1%)	1 (4%)	
> Urgency, n	383 (5%)	8 (29%)	
> Election, n	6823 (94%)	19 (68%)	
Redo surgery, n	568 (7.8%)	7 (25%)	0.005
Antiplatelets, n	1516 (21%)	7 (25%)	0.6
Inotropes, n	37 (0.51%)	1 (3.6%)	0.14
Diuretics, n	2639 (36%)	19 (68%)	< 0.001
Betablockers, n	2560 (35%)	8 (29%)	0.6
Antiarrhythmics, n	757 (10%)	2 (7.1%)	0.8
Antibiotics, n	205 (2.8%)	2 (7.1%)	0.18
Calcium channel antagonists, n	1026 (14%)	4 (14%)	0.9
Nitrates,n	842 (12%)	4 (14%)	0.8

ACE inhibitors, n	3197 (44%)	7 (25%)	0.055
Oral anticoagulants, n	995 (14%)	4 (14%)	0.9
Heparin, n	322 (4.4%)	2 (7.1%)	0.6
Previous cardiac surgery, n	417 (5.7%)	3 (10.7%)	0.4
Bilirubin, mg/dl	0.8 (0.6 – 1.1)	1.01 (0.66 – 1.51)	0.17
Intraoperative data			
CPB, n	6778 (94%)	25 (100%)	0.4
Cardioplegy, n	2838 (39%)	10 (36%)	0.8
Duration of aortic clamping, min	59 (47 – 75)	73 (55 – 98)	0.07
Duration of CPB, min	76 (62 – 95)	94 (90 – 104)	0.027
Outcomes			
Death, n	149 (2.05%)	14 (50%)	<0.001
ICU stay, days	1 (1 – 3)	20 (12 – 39)	<0.001
Hospital stay, days	6 (4 – 8)	42 (18 – 54)	<0.001
Creatinine peak, mg/dl	0.9 (0.75 – 1.12)	1.03 (0.77 – 1.72)	0.1
Blood loss in the first 12 h after surgery, ml	240 (180 – 350)	240 (160 – 380)	0.9
Total blood loss, ml	350 (220 – 500)	545 (350 – 610)	0.11
CVVH, n	139 (1.9%)	10 (36%)	< 0.001
RBC transfusions, n	0 (0 – 0)	2.5 (0 – 7.5)	< 0.001

FFP transfusions, n	0 (0 – 0)	0 (0 – 2)	< 0.001
PLT transfusions, n	0 (0 – 0)	0 (0 – 0)	<0.001
Hemoderivates, n	1516 (21%)	18 (64%)	< 0.001
Mechanical ventilation, hours	12 (8 – 16)	240 (72 – 360)	< 0.001
Neurologic injury type 1*, n	86 (1.2%)	2 (7.1%)	0.044
Neurologic injury type 2*, n	110 (1.5%)	1 (3.6%)	0.3
IABP, n	99 (1.4%)	1 (3.6%)	0.3
Perioperative AMI, n	114 (1.6%)	1 (3.6%)	0.4
Troponine peak value,	7.9 (4.8 – 13)	18.7 (5.2 – 31.6)	0.045
Atrial fibrillation, n	1242 (17%)	13 (46%)	< 0.001
Tracheostomy, n	85 (1.2%)	14 (50%)	< 0.001
Reintubation, n	91 (1.3%)	12 (43%)	< 0.001
Cardiogenic shock, n	148 (2%)	8 (29%)	< 0.001
Inotropes more than 48 hours, n	701 (9.6%)	13 (46%)	< 0.001
Pulmonary dysfunction, n	418 (5.7%)	16 (57%)	< 0.001

ACE, angiotensin converting enzyme; ACEF, age, creatinine, ejection fraction; AMI, acute myocardial infarction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVVH, continuous venovenous hemofiltration; FFP, fresh frozen plasma; LCOS, low cardiac output syndrome; MRSA, Methicillin Resistant Staphylococcus Aureus; IABP, intraaortic balloon pump; ICU,

intensive care unit; NYHA, New York Heart Association; PLT, platelets; RBC, red blood cells.

* Neurologic damage type I is defined as death due to stroke or hypoxic encephalopathy, new nonfatal stroke, or transient ischemic attack (TIA), or stupor or coma at the time of discharge. By neurologic damage type II we mean a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or a nonmetabolic seizure without evidence of focal injury. (17)

Table 3. Baseline, intraoperative, and postoperative data of patients who survived compared to patients who died during hospitalization. Continuous data are presented as media ± standard deviation, and categorical variables as number and percentage

Variable	Alive (N = 7150)	Dead (N = 163)	P-Value
Male gender, n	4603 (64%)	93 (57%)	0.054
Age, years	60 ± 13.7	69 ± 10.3	< 0.001
Height, cm	169 ± 9.2	165 ± 9	< 0.001
Weight, kg	72 ± 13.7	70 ± 15.9	0.03
BMI	25.3 ± 4	25.5 ± 5.1	0.8
Comorbidity			
> Active smoking, n	856 (12%)	10 (6.1%)	0.026
> COPD, n	1017 (14%)	85 (52%)	< 0.001
> Ejection fraction, %	55.8 ± 10.1	46.5 ± 13.5	< 0.001
> Ejection fraction <= 40%, n	737 (12%)	44 (40%)	< 0.001
> Vasculopathy, n	1067 (15%)	37 (23%)	0.008

> Arterial hypertension, n	2648 (37%)	58 (36%)	0.7
> Diabetes, n	702 (9.8%)	25 (15%)	0.024
> Angina, n	488 (6.8%)	13 (8%)	0.6
> Acute myocardial infarction, n	648 (9.1%)	29 (18%)	<0.001
> Euroscore standard	4 (3 – 6)	7 (6 -9)	< 0.001
> ACEF mortality risk	1.87 (1.4 – 2.4)	3.1 (2.1 – 6.5)	< 0.001
> Creatinine clearance, ml/h	80 (60.8 – 101.5)	48.5 (37.2 – 66.5)	< 0.001
> Stroke or transient ischemic attack, n, n	395 (5.5%)	9 (5.5%)	0.5
> Active bacterial endocarditis, n	132 (1.9%)	6 (3.7%)	0.13
> Creatinine, mg/dl	0.98 ± 0.57	1.38 ± 1.07	< 0.001
NYHA			< 0.001
> I, n	983 (20%)	2 (3%)	
> II, n	2504 (52%)	21 (30%)	
> III, n	1294 (27%)	37 (53%)	
> IV, n	71 (1%)	10 (14%)	
Preoperative IABP, n	174 (2.4%)	18 (11%)	< 0.001
Timing of intervention			< 0.001
> Emergency	57 (0.8%)	23 (14%)	
> Urgency, n	371 (5.2%)	20 (12%)	

> Election, n	6722 (94%)	120 (74%)	
Redo surgery, n	547 (7.7%)	28 (17%)	< 0.001
Antiplatelets, n	1498 (21%)	25 (15%)	0.09
Inotropes, n	30 (0.42%)	8 (4.9%)	< 0.001
Diuretics, n	2575 (36%)	83 (51%)	< 0.001
Betablockers, n	2526 (35%)	42 (26%)	0.013
Antiarrhytmics, n	733 (10%)	26 (16%)	0.021
Antibiotics, n	195 (2.7%)	12 (7.4%)	0.002
Calcium channel antagonists,	1013 (14%)	17 (10%)	0.21
Nitrates, n	822 (12%)	23 (14%)	0.3
ACE inhibitors, n	3150 (44%)	54 (33%)	0.007
Oral anticoagulants, n	979 (14%)	20 (12%)	0.6
Heparin, n	317 (4.4%)	7 (4.3%)	0.9
Previous cardiac surgery	303 (5.6%)	17 (10%)	0.009
Bilirubin, mg/dl	0.8 (0.6 – 1.1)	0.92 (0.65 – 1.6)	0.026
Intraoperative data			
CPB, n	6671 (94%)	132 (94%)	0.8
Cardioplegy, n	2801 (39%)	47 (29%)	0.007
Duration of aortic clamping, min	59 (47 – 75)	68 (50 – 82)	0.02
Duration of CPB, min	76 (62 – 95)	94 (76 – 116)	< 0.001

Outcomes			
ICU stay, days	1 (1 – 3)	9 (3 – 19)	< 0.001
Hospital stay, days	6 (4 – 8)	15 (7 – 33)	< 0.001
Creatinine peal value, mg/dl	0.9 (0.75 – 1.11)	1.27 (1 – 1.66)	< 0.001
Blood loss in the first 12 h after surgery, ml	240 (180 – 350)	300 (200 – 540)	< 0.001
Total blood loss, ml	350 (220 – 500)	500 (330 – 770)	0.005
CVVH, n	76 (1.1%)	73 (45%)	< 0.001
RBC transfusions, n	0 (0 – 0)	2 (0 – 7)	< 0.001
FFP transfusions, n	0 (0 – 0)	0 (0 – 4)	< 0.001
Platelet transfusions, n	0 (0 – 0)	0 (0 – 3)	< 0.001
Hemoderivates, n	1425 (20%)	109 (67%)	< 0.001
Mechanical ventilation, hours	12 (8 – 16)	72 (28 – 264)	< 0.001
Neurologic damage type 1*, n	71 (1%)	17 (10%)	< 0.001
Neurologic damage type 2*, n	97 (1.4%)	14 (8.6%)	< 0.001
IABP, n	97 (1.4%)	2 (1.2%)	0.9
Perioperative AMI, n	99 (1.4%)	16 (9.8%)	< 0.001
Troponine peak value,	7.8 (4.8 – 13)	18.9 (9.2-36)	< 0.001

Atrial fibrillation, n	1218 (17%)	37 (23%)	0.059
Tracheostomy, n	58 (0.8%)	41 (25%)	< 0.001
Reintubation, n	69 (0.97%)	34 (21%)	< 0.001
Cardiogenic shock, n	80 (1.1%)	76 (47%)	< 0.001
Inotropes more than 48 hours, n	626 (8.8%)	88 (54%)	< 0.001
Pulmonary dysfunction, n	360 (5%)	74 (45%)	< 0.001

ACE, angiotensin converting enzyme; ACEF, age, creatinine, ejection fraction; AMI, acute myocardial infarction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVVH, continuous venovenous hemofiltration; FFP, fresh frozen plasma; LCOS, low cardiac output syndrome; MRSA, Methicillin Resistant Staphylococcus Aureus; IABP, intraaortic balloon pump; ICU, intensive care unit; NYHA, New York Heart Association; PLT, platelets; RBC, red blood cells.

* Neurologic damage type I is defined as death due to stroke or hypoxic encephalopathy, new nonfatal stroke, or transient ischemic attack (TIA), or stupor or coma at the time of discharge. By neurologic damage type II we mean a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or a nonmetabolic seizure without evidence of focal injury. (17)

Table 4. Site of Methicillin Resistant Staphylococcus spp isolation.

Site of sampling	**MRS Aureus**	**Not Aureus MRS**
Bronchoalveolar secretions, n	21	1
Blood, n	9	100

Central venous catheter,n	7	31
Pleural effusion, n	1	1
Other, n	9	18

MRS, Methicillin Resistant Staphylococcus.

Table 5. Factors associated with Methicillin-resistant Staphylococcus Aureus (MRSA) infection at multivariate analysis.

Effect	Odds Ratio	95% Wald Confidence Limits	P	
COPD	4.356	1.382	13.729	0.012
Vasculopathy	3.365	1.097	10.319	0.034
Urgent or emergent surgery	6.301	1.984	20.008	0.002
Redo surgery	4.846	1.527	15.383	0.007
Diuretics	10.012	1.266	79.191	0.029

COPD, chronic obstructive pulmonary disease.

Table 6. Independent predictors of hospital mortality at multivariate analysis.

Effect	Odds Ratio	95% Wald Confidence Limits	P	
MRSA	20.519	4.143	101.626	0.0002
Acute myocardial infarction	2.472	1.315	4.646	0.005
Antiarrhythmics	2.454	1.289	4.672	0.006
CVVH	12.219	6.418	23.264	< 0.0001
Hemoderivates	2.959	1.612	5.432	0.0005

Neurologic damage type 2*	4.526	1.718	11.923	0.002
Tracheotomy	2.615	1.097	6.233	0.03
Reintubation	4.629	2.01	10.662	0.0003
Cardiogenic shock	16.665	8.47	32.791	< 0.0001
Pulmonary dysfunction	2.417	1.268	4.61	0.007

CVVH, continuous venovenous hemofiltration; MRSA, Methicillin Resistant Staphylococcus Aureus.

* Neurologic damage type I is defined as death due to stroke or hypoxic encephalopathy, new nonfatal stroke, or transient ischemic attack (TIA), or stupor or coma at the time of discharge. By neurologic damage type II we mean a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or a nonmetabolic seizure without evidence of focal injury. (17)

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