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ORIGINAL ARTICLE

Gram-negative rod bacteremia after cardiovascular surgery: Clinical features and prognostic factors☆

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KEYWORDS
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retrospective study

Abstract *Background/Purpose:* Our aim was to describe the clinical features and prognostic factors of Gram-negative rod bacteremia (GNRB) after cardiovascular surgery (CVS).
Methods: This retrospective observational study included adults with GNRB onset within 100 days after CVS at a single institution from April 2004 to May 2013. Clinical data regarding episodes of GNRB were collected from patients' medical charts. Those having polymicrobial bacteremia with a bacterium other than a GNR were excluded.
Results: Among 2017 CVS patients, GNRB occurred in 78. *Klebsiella*, *Pseudomonas aeruginosa*, *Enterobacter*, and *Escherichia coli* were the most commonly isolated organisms. Graft replacement was the most common surgical procedure in patients with GNRB after CVS (44.9%). Prophylaxis antibiotics were ampicillin/sulbactam (76.9%), and vancomycin (12.8%). The crude 90-day mortality rate was 21.8%, and the mean Acute Physiology and Chronic Health Evaluation II score was 15.6 (range, 3–39). In 34.6% of patients, the same GNR species were isolated from other samples within 30 days of GNRB occurrence. Multivariate analysis indicated that *P. aeruginosa* bacteremia [odds ratio (OR), 175; confidence interval (CI), 2.40–1270; $p = 0.0182$], Acute Physiology and Chronic Health Evaluation II scores of ≥ 25 (OR 76.2; CI 1.04–5580; $p = 0.0479$), and vancomycin for prophylaxis (OR 45.4; CI 1.02–202; $p = 0.0488$) were significant independent prognostic factors associated with death due to GNRB after CVS.

☆ Results from this study were presented, in part, at the 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona, Spain, May 10–13, 2014 (Abstract eP045).

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Conclusion: Graft replacement was the most common surgical procedure in patients with GNRB after CVS. Empirical antibiotics covering Gram-negative rods including *P. aeruginosa* should be considered if bacteremia is suspected in unstable patients after CVS.

Introduction

Gram-negative rod bacteremia (GNRB) after cardiovascular surgery (CVS) is a serious complication associated with morbidity and mortality.[1,2] However, no studies have systematically studied GNRB after CVS. Infections after CVS, such as surgical site infection and mediastinitis, are often caused by *Staphylococcus* spp.[3–5] Fowler et al[5] reported that in patients with bacteremia that developed within 90 days after CVS, *Staphylococcus* spp. accounted for 75.8% of causative organisms of bacteremia episodes and Gram-negative rods (GNRs) accounted for 18.8%. GNRB may be a frequent cause of inappropriate treatment, because GNRs are underestimated in bacteremia after CVS.

We aimed to describe the demographical, clinical, microbiological, and prognostic factors of GNRB after CVS.

Methods

Study design

We conducted a retrospective observational study at Tokyo Women's Medical University Hospital in Tokyo, Japan, a 1423-bed university-affiliated hospital, with 200 beds in the cardiovascular department, which is one of the largest institutes for cardiovascular disease. Clinical data regarding episodes of GNRB were collected from patients' medical charts. All adult cases of GNRB after CVS from April 2004 to May 2013 were included. The Ethics Committee at Tokyo Women's Medical University Hospital approved the study protocol (approval number 3013).

Definitions

An episode of GNRB was defined as an adult patient with at least one positive blood culture yielding any GNRs. Blood samples were drawn under sterile conditions and processed using the BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems, Towson, MD, USA) until March 11, 2011, and the BacT/ALERT 3D system (bioMérieux, Marcy l'Etoile, France) from April 2011 to May 2013. Blood samples were incubated for up to 7 days. GNRs were identified using GNR-Combo NC6.11J, NC6.12J, and NC3.12J (Siemens Healthcare Diagnostics, Deerfield, IL, USA). We defined the date of GNRB diagnosis as the day of sampling of positive blood culture. We enrolled patients for whom the number of days from CVS to GNRB diagnosis was within 100 days. If the patient had many episodes of GNRB, we included all episodes of GNRB and analyzed each episode separately. Basically ampicillin/sulbactam was used as prophylaxis antibiotics, and vancomycin was chosen for patients with β-lactam allergy or Methicillin-resistant Staphylococcus aureus colonization. The empiric antibiotic was considered "appropriate," if the treatment regimens included at least one antibiotic active *in vitro* against all identified pathogens. We considered antimicrobial therapy "inappropriate" if the drugs used did not have *in vitro* activity against the isolated strain, or if the patient did not receive any antibiotics empirically. If *in vitro* activity of the antibiotic was not tested, we defined it as "unknown." Bentall procedure was included in graft replacement (thoracic). We evaluated the species isolated from other sites within 30 days from when the blood culture was performed. If there was more than one sample from the same site, only the latest sample was enrolled.

Study population

Patients were observed from the day of GNRB diagnosis to the 90-day follow-up. The following data were obtained for all patients: age, sex, comorbidities, type of surgery, use of medical devices, source of bacteremia, empirical or definitive antibiotics, time period from surgery to bacteremia development, culture samples from any sites, Acute Physiology and Chronic Health Evaluation (APACHE) II score at the day blood cultures were performed, and crude mortality in 90 days. We determined the source of bacteremia after reviewing medical records written by the primary physicians and receiving agreement from the infectious disease physician. Exclusion criteria were patients younger than 20 years, being enrolled in another clinical trial, the presence of polymicrobial bacteremia with a bacterium other than a GNR, and the surgery type being catheter surgery.

Statistical analysis

Continuous data were compared using the Student t test and categorical data using Fisher's exact tests. Data were considered statistically correlated when $p < 0.05$. Multivariate analysis was used to determine the independent risk factors associated with mortality using forward stepwise logistic regression. All variables with $p < 0.1$ in univariate analysis were entered into the multivariate model. Statistical analyses were performed using *R*, version 3.0.2 (http://www.r-project.org/).

Results

Clinical features

Among 2017 CVS patients, 434 developed bacteremia. Gram-positive cocci were present in 267 (61.5%) patients

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(*Staphylococcus* spp. in 237 patients, *Streptococcus* spp. in 16 patients, and *Enterococcus* spp. in 14 patients), GNRs in 135 (31.1%) patients, Gram-positive rods in 29 (6.7%) patients, and Gram-negative cocci in three (0.7%) patients. The incidence of GNRB after CVS was 6.7% ($n = 135$). Of the 135 patients with GNRB, 78 were included in this study. Of the 135 patients, 57 were excluded because of being enrolled in other clinical trials ($n = 21$), bacteremia onset being $>$ 100 days after CVS ($n = 28$), and polymicrobial bacteremia with a bacterium other than a GNR ($n = 8$). Demographic and clinical characteristics of the 78 cases (61 survivors and 17 deaths) with GNRB after CVS are shown in Table 1. The mean age of the patients was 64.9 $\pm$ 11.2 years. Of the 78 patients, 35 (44.9%) underwent graft replacement, 18 (23.1%) isolated coronary artery bypass grafting, four (5.1%) coronary artery bypass grafting plus valve replacement, 19 (24.4%) isolated valve replacement, and two (2.6%) other surgery (1 removal of the left atrial myxoma, and 1 resection of pulmonary arterial aneurysm and closure of atrial septal defect).

Comorbidities included hypertension (43.6%), diabetes mellitus (25.6%), and chronic kidney disease (24.4%). Eight (10.3%) patients had previous CVS. At the onset of bacteremia, these patients had previously undergone urinary catheter placement (55.1%), central venous catheter placement (47.4%), intubation (43.6%), treatment with a vasopressor (32.1%), and dialysis (26.9%). The sources of bacteremia were the urinary tract (16.7%), mediastinum (10.3%), and peritoneum (6.4%); however, sources could not be identified in 56.4% ($n = 44$) of patients. Seventy-seven of 78 patients (98.7%) had prophylaxis antibiotics.

Reported prophylaxis antibiotics were ampicillin/sulbactam ($n = 60$; 76.9%), vancomycin ($n = 10$; 12.8%), ampicillin/sulbactam plus amikacin ($n = 2$), cefazolin ($n = 1$), vancomycin plus meropenem ($n = 1$), ampicillin ($n = 1$), arbekacin ($n = 1$), and unknown ($n = 2$). The median period from the day of surgery to the day of blood culture was 11 days (range, 2–94 days). GNRB occurred $<$ 7 days after CVS in 26.9% of patients and $<$ 14 days in 62.8% (Figure 1). A total of 89 GNRs were identified in the 78 patients (Table 2). *Klebsiella* spp. ($n = 22$; 24.7%), *Pseudomonas aeruginosa* ($n = 21$; 23.6%), *Enterobacter* spp. ($n = 18$; 20.2%), and *Escherichia coli* ($n = 11$; 12.4%) were the most commonly isolated organisms, accounting for 80.9% of all bacteremia episodes. There were three extended-spectrum β-lactamase-producing *Klebsiella* sp. (3.4%) and two carbapenem-resistant *P. aeruginosa* (2.2%). The empiric antibiotics were appropriate in 70.5% ($n = 55$), inappropriate in 14.1% ($n = 11$), and unknown in 15.4% ($n = 12$). The mean APACHE II score was 15.6 (range, 3–39), the crude 14-day mortality rate was 11.5%, and the crude 90-day mortality rate was 21.8%. The results of univariate and multivariate analyses are shown in Table 1. The incidence of GNRB $<$ 7 days after CVS was 47.1% in the death group and 21.3% in the survival group ($p = 0.0603$). *P. aeruginosa* bacteremia [odds ratio (OR), 175; confidence interval (CI), 2.40–1270; $p = 0.0182$], APACHE II scores of $\geq$ 25 (OR, 76.2; CI, 1.04–5580; $p = 0.0479$), and vancomycin prophylaxis (OR, 45.4; CI, 1.02–202; $p = 0.0488$) were independent prognostic factors associated with death due to GNRB after CVS. We compared the characteristics of patients with *P. aeruginosa* ($n = 21$) and non-*P. aeruginosa* bacteremia ($n = 57$). Statistically significant differences ($p < 0.05$) were shown in mortality rate (*P. aeruginosa* group 50.0% vs. non-*P. aeruginosa* group 12.1%, $p = 0.0171$), APACHE II score (30.0% vs. 5.2%, $p = 0.00979$), thoracic graft replacement (10.0% vs. 32.8%, $p = 0.0447$), the incidence of GNRB $<$ 7 days after CVS (45.0% vs. 19.0%, $p = 0.0203$), and dialysis (50.0% vs. 19.0%, $p = 0.0203$). The *P. aeruginosa* group had more frequency of hypertension (60.0% vs. 36.2%), diabetes mellitus (35.0% vs. 20.7%), chronic kidney diseases (40.0% vs. 19.0%), urinary catheterization (70.0% vs. 17.2%), and central venous catheterization (55.5% vs. 43.1%).

Same species from other sites

In 27 (34.6%) patients, the same species were isolated from 40 samples other than the blood within 30 days from when the blood culture was performed (Table 3). The same organisms were isolated from sputum ($n = 19$; 47.5%), catheter tips ($n = 8$; 20.0%), urine ($n = 5$; 12.5%), pharynx exudate ($n = 5$; 12.5%), skin ($n = 2$; 5.0%), and otorrhea ($n = 1$; 2.5%). In 27 patients, drug susceptibility of the organism isolated from the samples was the same as that of the blood in five (18.5%) patients, partially the same in two (7.4%) patients, and all different in 20 (74.1%) patients.

Discussion

This study analyzed the demographical, clinical, and microbiological features, as well as the outcomes and prognostic factors of GNRB after CVS. To the best of our knowledge, this is the first paper to report on GNRB after CVS specifically.

The incidence of GNRB after CVS observed among our patients was 6.7%. There were no such reports to describe the incidence of Gram-negative bacteremia after CVS. The frequency of GNR to all causative organisms of bacteremia was 31.4% in our study. The reported frequency of GNR after CVS varies from 18.8% to 60.0%.[2,5]

The mortality rate of GNRB after CVS observed among our patients was 21.8%. In a previous study, the mortality rate of GNRB was estimated at 12% in non-neutropenic patients[6] and 53.3% in intensive care unit patients.[7] In our study, the 14- and 90-day mortality rates were estimated; however, which day mortality rate used was not clearly described in previous studies.

Our study suggests that graft replacement was the most common surgical procedure in patients with GNRB after CVS. Among the 35 patients who underwent graft replacement, 14 (40.0%) underwent thoracoabdominal or abdominal aortic grafting. Therefore, we evaluated the reasons why GNRB occurs after graft replacement. Koratzanis et al[8] reported that graft replacement for abdominal aortic aneurysm causes bacterial translocation. The ischemia/reperfusion of gut mucosa during surgery may promote translocation of bacteria.[9] Further, microinjury to organs in the abdomen, such as the kidney or intestines, during surgery can be the entry site of GNRs, although there were no apparent cases.

We identified that 62.8% of GNRB cases occurred $<$ 14 days after CVS. The high GNRB incidence in the early phase

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Table 1 Characteristics and prognostic factors associated with death in 90 days in patients with GNRB after CVS

	Total (n = 78)	Death (n = 17)	Survived (n = 61)	Univariate analysis	Multivariate analysis OR (95% CI)
	64.9 ± 11.2	64.6 ± 10.8	65.0 ± 11.4		
Age >65 y	49	11 (64.7)	38 (62.3)	1	
Sex (male)	53	12 (70.6)	41 (67.2)	1	
BMI > 25	16	4 (23.5)	12 (19.7)	0.74	
EF < 40	6	3 (17.6)	3 (4.9)	0.127	
APACHE n score ≥ 25	9	7 (41.2)	2 (3.3)	0.000203	76.2 (1.04—5580)*
Type of surgery					
-Graft replacement	35	6 (35.3)	29 (47.5)	0.42	
Thoracic	21	2 (11.8)	19 (31.1)	0.134	
Thoracoabdominal	8	3 (17.6)	5 (8.2)	0.362	
Abdominal	6	1 (5.9)	5 (8.2)	0.58	
-CABG + valve replacement	4	1 (5.9)	3 (4.9)	1	
-Isolated CABG	18	6 (35.3)	12 (19.7)	0.201	
-Isolated valve procedure	19	4 (23.5)	15 (24.6)	1	
-Others	2	0	2 (3.3)	1	
Comorbidity					
-Hypertension	34	9 (52.9)	25 (41.0)	0.418	
-Diabetes mellitus	20	4 (23.5)	16 (26.2)	1	
-Chronic kidney disease	19	4 (23.5)	15 (24.6)	1	
-Hyperlipidemia	14	2 (11.8)	12 (19.7)	0.722	
-Previous cardiovascular disease	8	3 (17.6)	5 (8.2)	0.362	
-Malignancy	7	1 (5.9)	6 (9.8)	1	
-Cerebrovascular disorder	7	0	7 (11.5)	0.336	
-Bronchial asthma	3	1 (5.9)	2 (3.3)	0.527	
Devices					
-Urinary catheter	43	13 (76.5)	30 (49.2)	0.0565	
-Central venous catheter	37	11 (64.7)	26 (42.6)	0.169	
-Intubation	34	15 (88.2)	19 (31.1)	0.0000405	
-Vasopressor	25	9 (52.9)	16 (26.2)	0.0452	
-Dialysis	21	9 (52.9)	12 (19.7)	0.0117	
-IABP	4	2 (11.8)	2 (3.3)	0.205	
Organism					
-*Klebsiella* spp.	22	3 (17.6)	19 (31.1)	0.368	
-*Pseudomonas aeruginosa*	21	10 (58.8)	11 (18.0)	0.00171	175 (2.4—1270)*
-*Enterobacter* spp.	18	4 (23.5)	14 (23.0)	1	
-*Escherichia coli*	11	1 (5.9)	10 (16.4)	0.439	
Source of bacteremia					
-Urinary tract	13	0	13 (21.3)	0.0599	
-Mediastinum	8	2 (11.8)	6 (9.8)	1	
-Peritoneum	5	0	5 (8.2)	0.58	
-Lung	4	1 (5.9)	3 (4.9)	1	
-Catheter-related	3	0	3 (4.9)	1	
-Skin and soft tissue	1	0	1 (1.6)	1	
-Unknown	44	14 (82.4)	30 (49.2)	0.0251	
Prophylactic use of antimicrobial					
-Ampicillin/sulbactam	60	9 (52.9)	51 (83.6)	0.0188	
-Vancomycin	10	5 (29.4)	5 (8.2)	0.035	45.4 (1.02—202)*
Empirical antimicrobial therapy					
-Carbapenems	25	7 (41.2)	18 (29.5)	0.389	
-Fluoroquinolone	4	2 (11.8)	2 (3.3)	0.205	
Appropriate empirical therapy	55	10 (58.8)	45 (73.8)	0.018	
From CVS to GNRB < 7 d	21	8 (47.1)	13 (21.3)	0.0603	
The same species isolated from other sites within 30 d	27	7 (41.2)	20 (32.8)	0.571	

*$p < 0.05$.

APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; CABG = coronary artery bypass graft; CI = confidence interval; CVS = cardiovascular surgery; EF = ejection fraction; GNRB = Gram-negative rod bacteremia, IABP = intra-aortic balloon pump; OR = odds ratio; SD = standard deviation.

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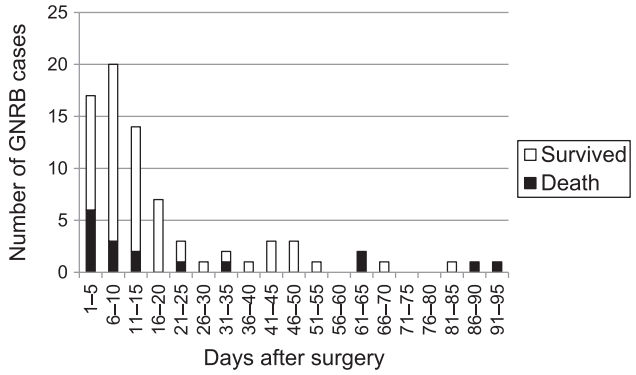

Figure 1. Occurrence and fatality rates of Gram-negative rod bacteremia. GNRB = Gram-negative rod bacteremia.

Table 2 Gram-negative rods isolated from blood ($N = 89$)

Organism	*n* (%)
Klebsiella spp.	22 (24.7)
Pseudomonas aeruginosa	21 (23.6)
Enterobacter spp.	18 (20.2)
Escherichia coli	11 (12.4)
Serratia marcescens	5 (5.6)
Acinetobacter spp.	3 (3.4)
Stenotrophomonas maltophilia	3 (3.4)
Prevotella spp.	2 (2.1)
Citrobacter spp.	1 (1.1)
Aeromonas spp.	1 (1.1)
Proteus spp.	1 (1.1)
Bacteroides spp.	1 (1.1)

after surgery may be due to heavy usage of medical devices such as urinary catheters, ventilators, or venous catheters that may cause urinary tract infection, ventilator-associated pneumonia, or catheter-related blood stream infection due to GNR. Although Gram-positive coccus may be the major causative organism, we should consider GNR as the causative organism when administering empirical antibiotic therapy, if we suspect bacteremia in the early phase after CVS. The median period from the day of surgery to the day of blood culture (occurrence of GNRB) was 11 days. The incidence of GNRB < 7 days after CVS was 47.1% in the death group and 21.3% in the survival group ($p = 0.0603$). Early-phase GNRB after CVS may be associated with a poor prognosis.

Table 3 Same organism from other samples ($N = 40$)

Samples	*n* (%)
Sputum	19 (47.5)
Catheter tip	8 (20.0)
Urine	5 (12.5)
Pharynx exudate	5 (12.5)
Skin	2 (5.0)
Otorrhea	1 (2.5)

When GNR is isolated from the blood culture, empirical antibiotic treatment must be initiated immediately, considering the species and antibiotic susceptibility of GNR. In a study, van Eck van der Sluijs et al[10] reported that an intravascular catheter tip colonized with Gram-negative microorganism was predictive of subsequent bacteremia in 19% of cases. In 34.6% of our patients, the same species were isolated from other samples within 30 days from the day the blood culture was performed. The most frequent sample was sputum, which accounted for 47.5% of all samples. As pneumoniae was determined to be the source of infection in only five cases, we speculate that unrecognized ventilator-associated pneumonia or a minor injury to the tracheal mucosa due to intubation may be the source of infection. Antibiotic susceptibility of other samples was the same in 18.5% patients, partially the same in 7.4%, and all different in 74.1%. It revealed that the antibiotic susceptibility of GNRs previously isolated from other sites was not in accordance with the susceptibility of GNRs isolated from the blood cultures in the current study. It is possible to assume this for two reasons. First, the new resistance occurred because of exposure of the same GNR strain to antibiotics. Second, the same species (other strain) was acquired from the hospital environment. Clonal delineation is needed. Our results indicate that GNRs isolated from any other sites (i.e., sputum) may help identify the species of GNR causing bacteremia.

In this study, sources of infection were not identified in as much as 55.8% of patients, which is not usual.[7,11] After CVS, patients are often intubated or sedated, making it difficult to identify symptoms and determine the identity of the infectious organ. Moreover, surgical site infection, mediastinitis, and catheter-related blood stream infection are generally caused by *Staphylococcus* spp.; therefore, clinicians may not consider them a source of GNRB. According to the literature, Gram-negative organisms account for 22–28.3% of mediastinitis,[12,13] and 20–30% of surgical site infections.[3,14]

This study provides evidence that several factors are associated with increased mortality from GNRB after CVS. These factors include *P. aeruginosa* bacteremia, APACHE II scores of ≥ 25, and vancomycin for prophylaxis. APACHE II scores of ≥ 25 and vancomycin for prophylaxis have not been reported as the prognostic factors in previous studies.

Previous reports of *Pseudomonas* bacteremia also have noted high mortality.[15] In our study, the patients with *P. aeruginosa* bacteremia might have had poor prognostic factors, as they had an increased frequency of hypertension, diabetes mellitus, and chronic kidney disease. Moreover, they also had an increased frequency of urinary catheterization, central venous catheterization, and dialysis. These medical devices could be risk factors for the infections caused by GNR. Further, as *P. aeruginosa* can be spread on hands of health care workers or by equipment that gets contaminated and is not properly cleaned, the patients with the devices had more chances to get *P. aeruginosa*. We emphasize the importance of infection control practices, especially hand hygiene and environmental cleaning, for preventing the spread of *P. aeruginosa* to reduce the mortality of patients after CVS.

According to the Infectious Diseases Society of America guideline for antimicrobial prophylaxis, vancomycin or

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clindamycin can be used as an alternative antimicrobial agent for β-lactam-allergic patients undergoing cardiac procedures, and addition of Gram-negative antibiotics for extended coverage may be prudent when Gram-negative pathogens are concerned.[16] Our study showed that vancomycin for prophylaxis is associated with high mortality in multivariable analysis, which indicates that prophylaxis antibiotic for CVS (i.e., graft replacement surgery) might cover Gram-negative organisms, too. Further investigation is needed.

Knaus et al[17] showed that nosocomial mortality of patients after surgery, whose APACHE II score was in the range of 25–29, is 37%. Conversely, our study showed that in patients with GNRB after CVS, an APACHE II score in the range of 25–29 indicates a 77.8% mortality rate. The high mortality observed in our study may have been caused by the hosts' unstable condition after CVS. We conclude that the APACHE II score suggests a higher mortality rate in patients with GNRB after CVS than in general populations, on the basis of the findings of a previous study.[17]

Previous studies showed that the factors associated with higher overall mortality included acute respiratory distress syndrome, septic shock, disseminated intravascular coagulation, anuria, the presence of a central venous catheter, the presence of a urinary catheter, an infection of unknown origin, inappropriate antibiotic treatment,[6] azotemia, and low or normal temperature.[15] In our study, the patients with urinary catheterization, an infection of unknown origin, and inappropriate empiric therapy have a high mortality, although not significant. However, the presence of a central venous catheter was not related to a high mortality.

This study has two limitations. First, the study involved a retrospective analysis with a small sample size at a single center. Second, the 90-day mortality included all deaths, which may have been due to not only GNRB, but also other factors such as low cardiac function, arrhythmia, or bleeding.

In conclusion, graft replacement was the most common surgical procedure in patients with GNRB after CVS. Early-phase GNRB after CVS may be associated with a poor prognosis. We identified that *P. aeruginosa* bacteremia, APACHE II scores of $\geq$ 25, and vancomycin for prophylaxis are independent prognostic factors associated with death due to GNRB after CVS. Empirical antibiotics covering GNRs, including *P. aeruginosa*, should be considered if bacteremia is suspected in unstable patients after CVS.

Conflicts of interest

The authors declare no conflicts of interest.

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