



# Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery

Ogawa, Masato

---

(Degree)

博士（保健学）

(Date of Degree)

2019-03-25

(Date of Publication)

2020-03-01

(Resource Type)

doctoral thesis

(Report Number)

甲第7500号

(URL)

<https://hdl.handle.net/20.500.14094/D1007500>

※ 当コンテンツは神戸大学の学術成果です。無断複製・不正使用等を禁じます。著作権法で認められている範囲内で、適切にご利用ください。



# 博 士 論 文

Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery

(心臓術後せん妄はフレイルを引き起こし、心血管イベントを予測する)

平成 31 年 1 月 9 日

神戸大学大学院保健学研究科保健学専攻

小川 真人

(Masato OGAWA)

## Abstract

*Background:* Postoperative delirium (POD) is a common and critical complication after cardiac surgery. However, the relationship between POD and postoperative physical frailty and the effect of both on long-term clinical outcomes have not been fully explored.

*Objective:* We aimed to examine the associations among POD, postoperative frailty, and major adverse cardiac events (MACE).

*Design:* This was a prospective cohort study.

*Methods:* We studied 329 consecutive patients undergoing elective cardiac surgery. The intensive care delirium screening checklist was used to assess POD. Postoperative frailty was defined by handgrip strength and walking speed. Patients were subsequently followed-up to detect MACE.

*Results:* POD was present in 13.2%, while the incidence of postoperative frailty was 27.0%. POD was independently associated with development of postoperative frailty (adjusted odds ratio = 2.98). During follow-up, MACE occurred in 14.1% of all participants. On multivariate Cox proportional hazard analysis, POD (adjusted hazard ratio (HR) = 3.36), postoperative frailty (HR = 2.21), postoperative complications (HR = 1.54), and left ventricular ejection fraction (HR = 0.95) were independently associated with increased risk of MACE.

*Limitations:* It is a single-center study with a risk of bias. We did not investigate follow up cognitive function.

*Conclusions:* POD was a predictor of postoperative frailty after cardiac surgery. Both postoperative frailty and POD were associated with the incidence of MACE, while POD was the stronger predictor of MACE. Thus, POD and frailty play critical roles in the risk stratification of patients undergoing cardiac surgery.

# Introduction

Delirium is defined as a temporary state of mental confusion and fluctuating consciousness, and it occurs in as many as 30% to 50% of patients after cardiac surgery [1].

A previous study showed that postoperative delirium (POD) increased with aging and resulted in a high rate of postoperative complications [2]. It was previously believed that delirium was a reversible cognitive impairment; however, recently, long-term adverse effects due to delirium were revealed.

Gottesman et al. [3] reported that POD after cardiac surgery was a strong predictor of mortality up to 10 years after the surgery. Another study also demonstrated that POD was associated with a significant decline in cognitive ability during the first year after cardiac surgery and no improvement was observed regardless of age [4]. Furthermore, patients with persistent delirium have been shown to be less likely to regain normal activities of daily living [5]. Thus, delirium can cause physical, mental, and social vulnerability in patients.

In contrast, many studies have described the relationship between frailty and cardiovascular disease [6-8]. Two studies recently showed that frailty in itself was a marker for adverse outcomes in patients with cardiovascular diseases [9, 10]. The exact cause of why frailty is related to adverse outcomes remains unknown. However, it may be attributable to the systemic effects of cardiovascular disease, such as activation of inflammatory and neurohumoral processes and limitation of physical activity[11]. Such mechanisms may lead to worse clinical outcomes.

Nevertheless, little evidence is available on the relationship between POD, postoperative frailty, and cardiovascular events. Elderly people with diminished preoperative physiologic reserves could be at a high risk of further reduction in their reserve capacity due to delirium. Thus, our hypothesis was that POD is independently associated with postoperative frailty after adjusting for other clinical characteristics and is a marker for subsequent clinical events. Therefore, we aimed to examine the associations among postoperative delirium, postoperative frailty, and long-term cardiovascular events.

# Materials and Methods

## *Study population*

Between September 2011 to December 2015, 368 consecutive patients who were admitted to Kobe University Hospital were screened. We enrolled a cohort of inpatients

in whom cardiopulmonary bypass was used in procedures, such as coronary artery bypass surgery (CABG), valve replacement or repair, or CABG with concomitant valve replacement or repair. Exclusion criteria included patients who underwent off-pump CABG; had neurological, peripheral vascular, orthopedic, or pulmonary disease; or had an incomplete assessment of delirium. All patients received postoperative rehabilitation starting the day after the surgery, according to the Japanese Circulation Society guidelines for rehabilitation in patients with cardiovascular disease [12]. The present study complied with the principles of the Declaration of Helsinki regarding investigations in human subjects and was approved by the Kobe University Institutional Review Board. Written informed consent was obtained from each patient before surgery.

### *Clinical characteristics of the patients*

Medical records were reviewed to obtain information about demographic characteristics. Baseline characteristics evaluated included age, sex, body mass index, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), brain natriuretic peptide (BNP) levels, serum hemoglobin levels, serum albumin levels, comorbidities, medications, and operative risk scores such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II [13]. Laboratory data and cardiac echocardiography were evaluated within 1 week before cardiac surgery and just before discharge. Operative clinical variables recorded included the type of cardiac operation (CABG, cardiac valve replacement, or combined CABG and valve replacement), the duration of cardiac surgery, cardiopulmonary bypass time, and aortic cross-clamp time in minutes.

Postoperative clinical variables recorded included hospital mortality, length of the intensive care unit (ICU) stay, and postoperative complications associated with surgery. We classified postoperative complications as follows: death (secondary to any major cardiac event); postoperative myocardial infarction; stroke; spinal cord injury; postoperative renal failure, defined as a new requirement for hemodialysis; cardiogenic syncope or serious ventricular dysrhythmias such as ventricular tachycardia that required defibrillation; septic shock; cardiac tamponade; hemorrhage requiring reoperation; and deep wound infection that affected the sternum, muscles, and/or mediastinum and required antibiotic treatment and/or surgical debridement.

The primary end points for this study were major adverse cardiac events (MACE) after discharge, which included cardiovascular death, non-fatal myocardial infarction (MI), hospital readmission for worsening heart failure or angina, and stroke. The patients were followed-up as outpatients, and the date and cause of any reported event determined during regularly scheduled outpatient visits was confirmed by review of hospital medical records.

## *Delirium assessment*

Delirium assessments were conducted every 8 hours by trained bedside nurses starting the first day after surgery up until 5 days after surgery using the Intensive Care Delirium Screening Checklist (ICDSC) [14]. The assessment of delirium was also checked retrospectively by research staff using the patients' medical records. The reliability and validity of the ICDSC for the detection of delirium have already been proven [14]. The ICDSC score ranges from 0 to 8, with a score of 4 or higher indicating clinical delirium. Patients with a diagnostic ICDSC score of  $\geq 4$  at any assessment point were considered likely to have delirium.

## *Measurement of frailty*

In this study, we assessed frailty by measuring handgrip strength and usual walking speed. Handgrip strength was measured with a grip strength dynamometer (T.K.K.5401; Takei Scientific Instruments Co., Ltd., Niigata, Japan) [15]. Three measurements were made of each hand, while watching for a possible Valsalva effect. We used the highest value of the right or left handgrip strength according to the standard protocol [16]. Walking speed was measured twice at usual speed as described elsewhere [17]. A 4-m section of the walkway was marked off by two lines, and space and time were allowed for acceleration and deceleration. Participants were allowed to use canes, but not assistance by a caregiver. Frailty was defined as diminished handgrip strength ( $<26$  kg for men and  $<18$  kg for women) and/ or usual walking speed ( $<0.8$  m/s) as described elsewhere and according to the definition of declining physical performance by the Asian working group for sarcopenia [18]. We assessed preoperative frailty within one week before surgery and postoperative frailty just before hospital discharge.

## *Statistical analysis*

We conducted statistical analyses after confirming that the data were normally distributed using the Shapiro-Wilk test. We compared clinical characteristics based on the presence or absence of MACE or postoperative frailty, and with or without POD using an independent *t*-test or chi-square test. To analyze factors affecting postoperative frailty and POD, a logistic regression analysis was used to examine each association between the incidence of frailty or POD and each variable. In this analysis, the incidence of frailty or POD was used as the dependent variable, while the clinical characteristics were independent variables. Factors in univariate analysis showing *P* values  $<0.10$  were entered simultaneously into a multivariate logistic regression model.

To analyze factors affecting MACE, multivariate analysis was performed using the Cox proportional-hazards regression model to simultaneously adjust for potential confounding variables. In this analysis, the incidence of MACE was used as the dependent variable, while independent variables included clinical characteristics, POD, and frailty. Subsequently, Kaplan-Meier survival statistics were used to examine the time to a first event, and a log-rank analysis was applied to compare event-free survival according to the incidence of POD and frailty. All statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at  $p < 0.05$ .

## Results

### *Patient characteristics*

Of the 368 patients, 42 were excluded from the study based on the inclusion and exclusion criteria. Of the 42 excluded patients, 10 refused to participate in this study, 4 did not complete the POD assessment, 15 had neurological disease, 10 had orthopedic issues, and 3 died in the hospital. Thus, 326 patients were included in the study (Fig 1). As shown in Table 1, the mean age of the patients was  $68.6 \pm 14.8$  years and 44.2% were female. Comorbidities present were hypertension (52.5%), diabetes mellitus (22.4%), dyslipidemia (28.8%), and atrial fibrillation (18.4%). The mean operation time was  $354.3 \pm 138.3$  min, and the incidence of postoperative complications was 12.3%. The median follow-up period was 311 days (interquartile range, 132-560).

**Table 1 Comparison of baseline characteristics in patients with or without MACE, and with or without postoperative frailty**

	Total	MACE (+)	MACE (-)	<i>t</i> or $\chi^2$ value	<i>p</i> value	Postoperative frailty (+)	Postoperative frailty (-)	<i>t</i> or $\chi^2$ value	<i>p</i> value
Number	326	46	280			88	238		
Age, years	68.6 ± 14.8	69.2 ± 15.4	68.1 ± 14.8	0.47	.64	77.5 ± 8.9	65.4 ± 15.3	6.71	<.0001
Female, n (%)	144 (44.2)	21 (45.7)	123 (43.9)	1.70	.19	54 (61.4)	90 (37.8)	22.72	<.0001
Body mass index, kg/m	23.1 ± 3.9	23.3 ± 4.3	23.0 ± 3.9	0.30	.76	22.3 ± 3.7	23.3 ± 4.0	-1.65	.11
Comorbidities									
Atrial fibrillation	60 (18.4)	11 (23.9)	49 (17.5)	1.66	.20	12 (13.6)	48 (20.2)	1.60	.19
Hypertension	171(52.5)	30 (65.2)	141 (50.4)	4.34	.03	48 (54.5)	123 (51.7)	2.33	.12
Dyslipidemia	94 (28.8)	18 (39.1)	76 (27.1)	3.62	.05	25 (26.1)	69 (29.0)	0.01	.98
Diabetes mellitus	73 (22.4)	15 (32.6)	58 (20.7)	3.62	.06	30 (34.1)	43 (18.1)	12.71	.0004
Euroscore II	6.3 ± 2.8	6.9 ± 3.4	6.2 ± 2.6	1.28	.20	6.9 ± 3.1	6.1 ± 2.5	1.52	.15
Types of surgery, n (%)									
Valve	206 (63.2)	25 (54.3)	181 (64.6)	1.80	.35	49 (55.7)	157 (66.0)	3.74	.15
Isolated CABG	29 (8.9)	5 (10.9)	24 (8.6)	—	—	9 (10.2)	20 (8.4)	—	—
Valve + CABG	91 (27.9)	16 (34.8)	75 (26.8)	—	—	30 (34.1)	57 (23.9)	—	—
Duration of surgery, min	354.3 ± 138.3	380.4 ± 126.4	348.1 ± 122.6	1.56	.12	333.1 ± 112.2	361.8 ± 126.8	-1.58	.11
Preoperative frailty, n (%)	22 (6.7)	6 (13.0)	16 (5.7)	2.70	.10	21 (23.9)	1 (0.4)	48.09	<.0001
Postoperative parameters									
Ejection fraction, %	60.0 ± 12.8	51.3 ± 15.2	61.1 ± 11.8	-4.80	<.0001	60.0 ± 12.8	60.1 ± 12.6	-0.02	.98



Laboratory data									
BNP, pg/ml	224.5 ± 369.2	363.1 ± 527.8	204.2 ± 337.2	2.50	.01	376.5 ± 532.0	176.2 ± 284.0	4.19	<.0001
eGFR, ml/min/1.73 m <sup>2</sup>	62.5 ± 22.2	60.0 ± 22.8	62.7 ± 22.1	-0.73	.47	53.0 ± 19.8	65.9 ± 22.1	-4.55	<.0001
Hemoglobin, g/dl	10.3 ± 1.18	10.2 ± 1.18	10.3 ± 1.13	0.35	.72	10.3 ± 1.2	10.2 ± 1.2	0.63	.53
Albumin, g/dl	3.1 ± 0.4	3.06 ± 0.38	3.11 ± 0.40	-0.74	.46	3.0 ± 0.4	3.1 ± 0.4	-2.28	.04
Medication, n (%)									
β-blocker	182 (55.8)	26 (56.5)	156 (55.7)	0.11	.74	47 (53.4)	135 (56.7)	0.07	.79
ACE-I / ARB	95 (29.1)	14 (30.4)	81 (28.9)	0.03	.87	25 (28.4)	70 (29.4)	0.11	.74
CCB	69 (21.2)	13 (28.3)	56 (20.0)	1.83	.18	15 (17.0)	54 (22.7)	1.83	.18
Diuretics	127 (39.0)	23 (50.0)	104 (37.1)	3.39	.07	38 (43.2)	89 (37.4)	2.06	.15
Length of ICU stay, day	2.4 ± 3.0	3.0 ± 1.4	2.3 ± 2.0	1.83	.27	3.1 ± 3.7	2.1 ± 2.1	2.35	.02
POD, n (%)	43 (13.2)	13 (28.3)	30 (10.7)	15.7	<.0001	19 (23.8)	28 (12.0)	5.93	.001
Postoperative complication, n (%)	40 (12.3)	10 (21.7)	30 (10.7)	9.70	.001	13 (14.8)	27 (11.3)	0.39	.53
Postoperative frailty, n (%)	88 (27.0)	30 (65.2)	58 (20.7)	12.6	<.0001	—	—	—	—
Postoperative MACE, n (%)	46 (14.1)	—	—	—	—	22 (25.0)	24 (10.1)	10.60	.0013

MACE: major cardiac adverse event; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; CABG: coronary artery bypasses grafting; ICU: intensive care unit; POD: postoperative delirium

Data are expressed as mean ± standard deviation or number (percentage).

### *Incidence of POD after surgery*

In our cohort, POD occurred in 44 patients (13.4%) according to the ICDSC criteria (Table.2). Individuals with POD were much older than non-POD patients (POD vs. non-POD;  $72.8 \pm 12.6$  vs.  $67.8 \pm 14.7$  years) and had lower preoperative eGFR ( $50.7 \pm 20.5$  vs.  $60.7 \pm 21.6$  ml/min/1.73 m<sup>2</sup>;  $p < 0.05$  for each). Patients with POD stayed significantly longer in the ICU at a mean of  $4.3 \pm 5.2$  days compared with non-POD patients ( $2.0 \pm 1.5$  days;  $p < 0.0001$ ). The prevalence of preoperative frailty was 18.6% in the patients with POD, while 4.9% in the patients with non-POD ( $p = 0.003$ ). On the other hand, preoperative BNP and LVEF, comorbidities, and type of surgery were not significantly different between the two groups. In multivariate analysis of risk factors for the development of POD, length of ICU stay and preoperative frailty remained statistically significant after adjustment for other confounding factors ( $p < 0.05$  for each) (Table.3)

**Table 2 Comparison of preoperative and intraoperative risk factors for delirium**

	Total	Delirium (+)	Delirium (-)	<i>t</i> or $\chi^2$ value	<i>p</i> value
Number	326	43 (13.2)	283 (86.8)		
Age, years	68.6 ± 14.8	72.8 ± 12.6	67.8 ± 14.7	2.18	.03
Female, n (%)	144 (44.2)	18 (41.9)	126 (44.5)	0.03	.85
Body mass index, kg/m	24.2 ± 3.9	24.2 ± 3.7	24.1 ± 4.0	0.07	.95
Comorbidities					
Atrial fibrillation	60 (18.4)	13 (30.2)	47(16.6)	2.73	.11
Hypertension	171(52.5)	27 (62.8)	144 (50.9)	0.60	.44
Dyslipidemia	94 (28.8)	14 (32.6)	80 (28.3)	0.02	.88
Diabetes mellitus	73 (22.4)	8 (18.6)	65 (23.0)	0.75	.39
Euroscore II	6.3 ± 2.8	6.6 ± 2.7	6.3 ± 2.8	0.73	.47
Ejection fraction, %	62.8 ± 10.8	59.9 ± 13.7	63.4 ± 12.4	-1.33	.18
Laboratory data					
BNP, pg/ml	171.2 ± 220.8	212.8 ± 199.9	165.5 ± 270.9	0.79	.43
eGFR, ml/min/1.73 m <sup>2</sup>	59.2 ± 21.7	50.7 ± 20.5	60.7 ± 21.6	-2.89	.004
Hemoglobin, g/dl	12.5 ± 1.9	12.1 ± 1.8	12.6 ± 2.0	-1.37	.17
Albumin, g/dl	3.9 ± 0.5	3.9 ± 0.5	4.0 ± 0.5	-1.08	.28
Medication, n (%)					
β-blocker	134 (41.1)	20 (46.5)	114 (40.3)	0.37	.54
ACE-I / ARB	155 (47.5)	25 (58.1)	130 (45.9)	2.18	.14
CCB	105 (32.2)	12 (27.9)	93 (32.9)	0.22	.64
Diuretics	129 (39.6)	19 (44.2)	110 (38.9)	0.25	.62
Preoperative frailty, n (%)	22 (6.7)	8 (18.6)	14 (4.9)	9.00	.003
Types of surgery, n (%)					
Valve	206 (63.2)	29 (67.4)	177 (62.5)	0.54	.77
Isolated CABG	29 (8.9)	4 (9.3)	25 (8.8)		
Valve + CABG	91 (27.9)	10 (23.3)	81 (28.6)		
Duration of surgery, min	354.3 ± 138.3	390.7 ± 138.3	344.8 ± 112.5	2.4	.02
Duration of CPB, min	179.5 ± 75.2	191.1 ± 77.1	175.7 ± 69.3	1.28	.20
Aortic cross-clamp time, min	108.9 ± 68.3	114.3 ± 64.4	98.7 ± 68.0	1.99	.05

Length of ICU stay, day	2.4 ± 3.0	4.3 ± 5.2	2.0 ± 1.5	4.91	< .0001
-------------------------	-----------	-----------	-----------	------	---------

BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; CABG: coronary artery bypasses grafting; CPB: cardiopulmonary bypass; ICU: intensive care unit

Data are expressed as mean ± standard deviation or number (percentage).

**Table 3 Univariate and multivariate analysis of risk factors for development of postoperative delirium**

Variables	Univariate model		Multivariate model	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.02 (1.01-1.41)	.02	1.01 (0.98-1.12)	.22
Sex, female	0.94 (0.50-1.78)	.85		
eGFR	0.98 (0.95-0.99)	.004	0.98 (0.97-1.02)	.18
Duration of surgery	1.01 (1.00-1.02)	.02	1.00 (0.99-1.00)	.28
ICU stay	1.28 (1.06-3.10)	.001	1.15 (1.04-1.97)	.02
Preoperative frailty	4.00 (2.04-4.35)	<.0001	2.85 (1.19-4.26)	.03

eGFR: estimated glomerular filtration rate; ICU: intensive care unit; OR, odds ratio; CI, confidence interval.

### *Postoperative frailty and its predictors*

As shown Table 1, the incidence of postoperative frailty was 27.0% (88 of 326 patients). Patients with POD had an approximately twice increased risk of postoperative frailty (23.8% vs. 12.0%;  $p < 0.0001$ ). In multivariate analysis, POD [adjusted odds ratio (OR) =2.98; 95% confidence interval (CI): 1.46-6.20], age (adjusted OR=1.09; 95% CI: 1.03-1.29), BNP level (adjusted OR=1.00; 95% CI: 1.00-1.03), and preoperative frailty (adjusted OR=3.70; 95% CI: 1.26-12.10) were independently associated with developing postoperative frailty after adjusting for potential confounders (Table 4).

**Table 4** Univariate and multivariate analysis of risk factors for postoperative frailty

Variables	Univariate model		Multivariate model	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.10 (1.03-1.39)	<.0001	1.09 (1.03-1.29)	<.0001
Sex, female	2.21 (1.00-4.79)	.04	2.98 (1.75-6.74)	.02
BMI	0.93 (0.79-1.04)	.16	—	—
Diabetes mellitus	2.62 (1.46-4.70)	.001	2.04 (0.79-5.20)	.14
eGFR	0.97 (0.60-0.99)	<.0001	0.97 (0.94-1.01)	.07
Albumin	0.68 (0.21-1.14)	.13	—	—
BNP	1.00 (1.00-1.02)	.004	1.00 (1.00-1.03)	.02
ICU stay	1.13 (0.98-1.99)	.10	—	—
POD	3.73 (2.13-6.68)	<.0001	2.98 (1.46-6.20)	.002
Preoperative frailty	15.75 (6.37-44.84)	.16	3.70 (1.26-12-10)	.02

eGFR: estimated glomerular filtration rate; BMI: body mass index; BNP: brain natriuretic peptide; ICU: intensive care unit; POD: postoperative delirium; OR, odds ratio; CI, confidence interval.

### *Results for MACE*

In this study, MACE after discharge occurred in 14.1% (46 of 326) of patients during follow up. The MACE were 4 events of MI, 29 events of heart failure, 8 events of stroke, and 5 events of cardiovascular death. Univariate associations with MACE after cardiac surgery are shown in Table 1. The presence of hypertension ( $p=0.03$ ), low preoperative cardiac function ( $p<0.0001$ ), high BNP levels ( $p=0.01$ ), and postoperative complications ( $p=0.001$ ) were significantly associated with the development of MACE, while age, the use of cardioprotective medications, and types of surgery were not associated with the incidence of MACE. POD was significantly associated with a high incidence of MACE (28.3% vs. 10.7%;  $p<0.0001$ ). Prevalence of postoperative frailty was 65.2% in the MACE group and 20.7% in the non-MACE group, indicating that the likelihood of MACE in frail patients was 3 times higher compared with that in the non-frail patients ( $p<0.0001$ ), while preoperative frailty was not statistically significant

for predicting MACE. The multivariate Cox proportional hazard model identified POD [adjusted hazard ratio (HR)=3.36; 95% CI: 1.32-7.32], postoperative frailty (adjusted HR=2.21; 95% CI: 1.01-4.82), postoperative complications (adjusted HR=1.54; 95% CI: 0.64-3.43), and postoperative LVEF (adjusted HR=0.95; 95% CI: 0.93-0.98) as independent predictors of MACE (Table 5).

The event-free survival curves of the four groups stratified by POD and postoperative frailty are shown in Fig 2. The Kaplan Meier analysis showed that POD and frailty were significantly associated with the incidence of MACE (Log-rank test  $p=0.0036$ ).

**Table 5 Independent predictors of MACE for patients undergoing cardiac surgery (Cox-hazard analysis)**

Variables	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Age	1.01 (0.98-1.03)	.72	—	—
Sex, female	1.51 (0.82-2.80)	.19	—	—
POD	4.70 (2.31-9.12)	<.0001	3.36 (1.32-7.82)	.016
Postoperative frailty	2.39 (1.20-4.78)	.01	2.21 (1.01-4.82)	.047
Hypertension	1.61 (0.85-3.17)	.14	—	—
Diabetes mellitus	1.61 (0.82-3.02)	.16	—	—
Dyslipidemia	1.43 (0.76-2.64)	.26	—	—
BNP	1.01 (1.00-1.01)	.02	1.00 (1.00-1.00)	.62
Postoperative complication	2.45 (1.19-4.76)	.02	1.54 (0.64-3.43)	.01
LVEF	0.95 (0.93-0.97)	<.0001	0.95 (0.93-0.98)	.0003
Diuretics	1.66 (0.91-3.05)	.09	1.22 (0.56-2.69)	.62

POD: postoperative delirium; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction

## Discussion

To the best of our knowledge, this is the first study to demonstrate the relationship between POD, postoperative frailty, and cardiovascular events in patients undergoing cardiac surgery. We found that both POD and postoperative frailty were independently associated with a worse clinical prognosis after adjustment for confounding variables.

It was reported that the incidence of POD after cardiac surgery varied with the type of cardiac surgery and ranged from 10% to 80% [19]. In our cohort, the incidence of POD was 14.1%, which is lower than that of other studies [20]. A possible explanation is that the our study included only cases of elective surgery and excluded emergency or urgent surgery in patients at a high risk of POD [20]. Furthermore, the mean age of our cohort was lower ( $64.9 \pm 16.2$  years) than that of previous studies [21]. Systematic review has shown that increasing age is the most important risk factor for POD [22]. Taken together, it is conceivable that our cohort comprised patients with a relatively low risk of delirium.

The pathophysiology of delirium has not been fully clarified; however, neuroinflammation and endothelial dysfunction have been identified as factors leading to an increased risk of delirium [23]. We showed that duration of surgery was significantly longer in the patients with POD. Our result is in line with a previous study that demonstrated that POD was independently associated with longer surgery duration [24]. Prolonged duration of surgery led to longer cardiopulmonary bypass (CPB) times and aortic cross-clamp time. During cardiac surgery using cardiopulmonary bypass, neuroinflammatory damage of the brain may occur due to microembolism, reduced cerebral flow, and fluid shift. These neurotransmitters may be responsible for the occurrence of POD in our cohort.

In contrast, it is well known that cognitive impairment after delirium is very common and persists for at least 1 year [4]. O'Donnell et al. [25] showed that cognitive dysfunction was associated with an increased risk of cardiovascular events, which was similar to that in patients with a previous stroke. Furthermore, decline of cognitive function causes several unfavorable conditions, such as poor compliance with medication, daily self-weighing, and symptom monitoring; increasing depression symptoms; and decline of social activity and physical function [26-28]. These findings would explain why POD was strongly associated with increased MACE in the present study. Moreover, heart failure was the most frequent cause of MACE. Presuming that

the difficulty of self-management may worsen heart failure, it is reasonable that POD was significantly associated with increased MACE. Furthermore, patients with POD were older, more likely to have a lower serum eGFR level, and more physically frail than those without POD. These background factors that cause POD due to a decreased total reserve capacity and vulnerability also affect the occurrence of MACE, not only POD itself.

Postoperative frailty was also an independent predictor of MACE in this study. Recently, several studies have investigated the relationship between frailty and worse outcomes such as falls and fractures, hospitalization, low quality of life, and high mortality in the general elderly population and in patients with heart failure [10, 29, 30]. Nevertheless, this is the first report to investigate frailty after cardiac surgery and its impact on prognosis. Frailty is considered to be a result of reduced physiological capacity [31]; it is caused by multiple factors, such as malnutrition, physical activity limitation, and cachexia, and can lead to unmanageable dysregulation of homeostasis. Thus, it is not surprising that the patients with frailty had negative health outcomes, and our results are in line with previous studies that demonstrated frailty in patients with heart failure [10]. On the contrary, preoperative frailty was not a predictor of MACE after discharge. It was thought that declining physical function due to delirium is more important and implicates the onset of MACE after discharge. Postoperative frailty caused decreased ability to mobilize and ambulate, and diminished physiological reserve and capacity to maintain homeostasis [32]. We think that these mechanisms partly explain the occurrence of MACE. In contrast, we had previously reported that low preoperative physical function was an independent predictor of POD after cardiac surgery [33]. Thus, delirium is thought to be both a cause and consequence of frailty.

It was also notable that POD was a stronger predictor of MACE than postoperative frailty. A previous study showed that cognitive impairment due to poor self-care management, defined as an inadequate decision-making process, was common in heart failure and may cause MACE [34]. Poor self-care management and confidence can be conducive to further functional limitation and frailty. Our findings underscore that intervention for prevention or treatment of POD is more important for frail patients.

In multivariate analysis, low LVEF and major postoperative complications were also identified as independent predictors of MACE. Uthamalingam et al. [35] reported the relationship between acute delirium and hospital readmissions with acute decompensated heart failure. In accordance with our results, they demonstrated that low LVEF and delirium were independent predictors of readmission. It is well known that



patients with severe cardiac dysfunction have a higher risk of death [36]. In addition, it is interesting to note that Georgiadis et al.[37] have demonstrated that a decline in LVEF is related to partially diminished cerebrovascular reactive dilatory capacity in patients with chronic heart failure. We did not investigate brain metabolism in this study; however, a decline in cerebrovascular reserve capacity due to attenuated cardiac function could be responsible for POD and cognitive dysfunction after cardiac surgery. The effects of these mechanisms can be observed in part by the significant increase in the incidence of MACE in patients with low LVEF.

Various treatments for delirium have been suggested, including antipsychotic agents, almost none of which have been effective [19]. Thus, we should focus on the prevention of delirium rather than its treatment, especially because Vidán et al. [38] demonstrated that a multicomponent non-pharmacological intervention for preventing delirium was effective and improved quality of care. In their study, the interventions to prevent delirium, included education, orientation, sleep preservation, nutritional support, and early mobilization. It is our firm belief that, particularly among such multicomponent interventions, early mobilization is important and essential to prevent delirium and functional decline especially for older patients or patients with renal failure. Furthermore, because the long-term care of patients who develop POD is often overlooked, there is a need for long-term follow-up and education of caregivers to aid in the self-management of heart failure. Further studies are required to confirm the effectiveness of such early intervention.

### *Study limitations*

There are some limitations to this study. It is a single-center study with a risk of bias. We could not analyze age- or sex-related differences because of our small sample size. We investigated baseline cognitive function from all patients, but did not reassess them during follow up. The patients with POD had persistent cognitive impairment [4], although the details of cognitive deficit were unclear. We also used ICDSC to detect POD, whose validity and reliability in the detection of delirium has already been proven. Nevertheless, it was reported that the specificity of the ICDSC is lower than that of other screening tools such as the Confusion-Assessment-Method for the ICU[14]. Therefore, the incidence of POD might have been underestimated in our cohort.

## Conclusion

POD was an independent predictor of the incidence of postoperative frailty after cardiac surgery. Both postoperative frailty and POD were strongly associated with MACE at 1 year after surgery, while POD was the stronger predictor of MACE than frailty. Thus, POD and frailty play extremely important roles in the risk stratification of patients undergoing cardiac surgery. A multicomponent intervention to prevent delirium and frailty is a matter of considerable urgency.

## Acknowledgments

We thank the staff members of Kobe University Hospital who collaborated in this study.

## Funding statement

This study was supported by a JSPS KAKENHI grant, number JP17K01500.

## Competing interests

The authors have declared that no competing interests exist.

## References

1. Brown CH. Delirium in the cardiac surgical ICU. *Curr Opin Anaesthesiol.* 2014;27(2):117-22. Epub 2014/02/12. doi: 10.1097/aco.0000000000000061. PubMed PMID: 24514034; PubMed Central PMCID: PMC4156112.
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr., et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Jama.* 2004;291(14):1753-62. Epub 2004/04/15. doi: 10.1001/jama.291.14.1753. PubMed PMID: 15082703.
3. Gottesman RF, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, et al. Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol.* 2010;67(3):338-44. Epub 2010/04/08. doi: 10.1002/ana.21899. PubMed PMID: 20373345; PubMed Central PMCID:

PMCPMC3723404.

4. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30-9. Epub 2012/07/06. doi: 10.1056/NEJMoa1112923. PubMed PMID: 22762316; PubMed Central PMCID: PMCPMC3433229.
5. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc*. 58. United States 2010. p. 643-9.
6. Reeves GR, Whellan DJ, Patel MJ, O'Connor CM, Duncan P, Eggebeen JD, et al. Comparison of Frequency of Frailty and Severely Impaired Physical Function in Patients  $\geq 60$  Years Hospitalized With Acute Decompensated Heart Failure Versus Chronic Stable Heart Failure With Reduced and Preserved Left Ventricular Ejection Fraction. *Am J Cardiol*. 2016;117(12):1953-8. Epub 2016/05/10. doi: 10.1016/j.amjcard.2016.03.046. PubMed PMID: 27156830; PubMed Central PMCID: PMCPMC4943325.
7. White HD, Westerhout CM, Alexander KP, Roe MT, Winters KJ, Cyr DD, et al. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: Insights from the Targeted platelet Inhibition to clarify the Optimal strategy to medically manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Eur Heart J Acute Cardiovasc Care*. 2016;5(3):231-42. Epub 2015/04/22. doi: 10.1177/2048872615581502. PubMed PMID: 25897147.
8. Chainani V, Shaharyar S, Dave K, Choksi V, Ravindranathan S, Hanno R, et al. Objective measures of the frailty syndrome (hand grip strength and gait speed) and cardiovascular mortality: A systematic review. *Int J Cardiol*. 2016;215:487-93. Epub 2016/05/02. doi: 10.1016/j.ijcard.2016.04.068. PubMed PMID: 27131770.
9. Yamada S, Japan NUGSoMDoRSN, Kamiya K, Japan NUGSoMPiPaOTN, Kono Y, Banbuntane Hotokukai Hospital Department of Rehabilitation FHUNJ. Frailty may be a risk marker for adverse outcome in patients with congestive heart failure. *ESC Heart Failure*. 2015;2(3):168-70. doi: 10.1002/ehf2.12052.
10. Lo AX, Donnelly JP, McGwin G, Jr., Bittner V, Ahmed A, Brown CJ. Impact of gait speed and instrumental activities of daily living on all-cause mortality in adults  $\geq 65$  years with heart failure. *Am J Cardiol*.

- 2015;115(6):797-801. Epub 2015/02/07. doi: 10.1016/j.amjcard.2014.12.044. PubMed PMID: 25655868; PubMed Central PMCID: PMC4474480.
11. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? *Aging Cell*. 2017. Epub 2017/03/08. doi: 10.1111/accel.12581. PubMed PMID: 28266167.
12. Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). *Circ J*. 78. Japan2014. p. 2022-93.
13. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4):734-44; discussion 44-5. Epub 2012/03/02. doi: 10.1093/ejcts/ezs043. PubMed PMID: 22378855.
14. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001;27(5):859-64. Epub 2001/06/30. PubMed PMID: 11430542.
15. Shimada H, Suzuki T, Suzukawa M, Makizako H, Doi T, Yoshida D, et al. Performance-based assessments and demand for personal care in older Japanese people: a cross-sectional study. *BMJ Open*. 2013;3(4). Epub 2013/04/13. doi: 10.1136/bmjopen-2012-002424. PubMed PMID: 23578683; PubMed Central PMCID: PMC3641481.
16. Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci*. 2000;55(3):M168-73. Epub 2000/05/05. PubMed PMID: 10795731.
17. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-94. Epub 1994/03/01. PubMed PMID: 8126356.
18. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*. 2014;15(2):95-101. Epub 2014/01/28. doi: 10.1016/j.jamda.2013.11.025. PubMed PMID: 24461239.
19. Sockalingam S, Parekh N, Bogoch, II, Sun J, Mahtani R, Beach C, et al. Delirium in the postoperative cardiac patient: a review. *J Card Surg*. 20.

United States 2005. p. 560-7.

20. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009;119(2):229-36. Epub 2009/01/02. doi: 10.1161/circulationaha.108.795260. PubMed PMID: 19118253; PubMed Central PMCID: PMC2735244.
21. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. *Crit Care Med*. 2015;43(1):40-7. Epub 2014/09/25. doi: 10.1097/ccm.0000000000000625. PubMed PMID: 25251759.
22. Hollinger A, Siegemund M, Goettel N, Steiner LA. Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace? *J Cardiothorac Vasc Anesth*. 2015;29(6):1677-87. Epub 2015/10/13. doi: 10.1053/j.jvca.2014.08.021. PubMed PMID: 26456271.
23. Hughes CG, Patel MB, Pandharipande PP. Pathophysiology of acute brain dysfunction: what's the cause of all this confusion? *Curr Opin Crit Care*. 2012;18(5):518-26. Epub 2012/09/04. doi: 10.1097/MCC.0b013e328357effa. PubMed PMID: 22941208.
24. Zhang WY, Wu WL, Gu JJ, Sun Y, Ye XF, Qiu WJ, et al. Risk factors for postoperative delirium in patients after coronary artery bypass grafting: A prospective cohort study. *J Crit Care*. 2015;30(3):606-12. Epub 2015/02/25. doi: 10.1016/j.jcrc.2015.02.003. PubMed PMID: 25708120.
25. O'Donnell M, Teo K, Gao P, Anderson C, Sleight P, Dans A, et al. Cognitive impairment and risk of cardiovascular events and mortality. *Eur Heart J*. 2012;33(14):1777-86. Epub 2012/05/04. doi: 10.1093/eurheartj/ehs053. PubMed PMID: 22551598.
26. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med*. 2001;161(14):1703-8. Epub 2001/08/04. PubMed PMID: 11485502.
27. Cacciatore F, Abete P, Ferrara N, Calabrese C, Napoli C, Maggi S, et al. Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. *J Am Geriatr Soc*. 1998;46(11):1343-8. Epub 1998/11/11. PubMed PMID: 9809754.
28. Alosco ML, Spitznagel MB, Cohen R, Raz N, Sweet LH, Josephson R, et al. Decreased physical activity predicts cognitive dysfunction and reduced

cerebral blood flow in heart failure. *J Neurol Sci.* 2014;339(1-2):169-75. Epub 2014/03/04. doi: 10.1016/j.jns.2014.02.008. PubMed PMID: 24581672; PubMed Central PMCID: PMC4009239.

29. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Norman PE, Flicker L. Depression, frailty, and all-cause mortality: a cohort study of men older than 75 years. *J Am Med Dir Assoc.* 2015;16(4):296-300. Epub 2014/12/17. doi: 10.1016/j.jamda.2014.10.023. PubMed PMID: 25499429.

30. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. *Gerontologist.* 2012;52(5):619-31. Epub 2012/01/06. doi: 10.1093/geront/gnr135. PubMed PMID: 22217462.

31. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol.* 2014;63(8):747-62. Epub 2013/12/03. doi: 10.1016/j.jacc.2013.09.070. PubMed PMID: 24291279; PubMed Central PMCID: PMC4571179.

32. Lee DH, Butz KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation.* 2010;121(8):973-8. Epub 2010/02/18. doi: 10.1161/circulationaha.108.841437. PubMed PMID: 20159833.

33. Ogawa M, Izawa KP, Satomi-Kobayashi S, Kitamura A, Tsuboi Y, Komaki K, et al. Preoperative exercise capacity is associated with the prevalence of postoperative delirium in elective cardiac surgery. *Aging Clin Exp Res.* 2017. Epub 2017/03/01. doi: 10.1007/s40520-017-0736-5. PubMed PMID: 28243862.

34. Kim JS, Hwang SY, Shim JL, Jeong MH. Cognitive Function and Self-Care in Patients with Chronic Heart Failure. *Korean Circ J.* 2015;45(4):310-6. Epub 2015/08/05. doi: 10.4070/kcj.2015.45.4.310. PubMed PMID: 26240585; PubMed Central PMCID: PMC4521109.

35. Uthamalingam S, Gurm GS, Daley M, Flynn J, Capodilupo R. Usefulness of acute delirium as a predictor of adverse outcomes in patients >65 years of age with acute decompensated heart failure. *Am J Cardiol.* 2011;108(3):402-8. Epub 2011/07/16. doi: 10.1016/j.amjcard.2011.03.059. PubMed PMID: 21757045.

36. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis.

Eur Heart J. 2012;33(14):1750-7. Epub 2011/08/09. doi: 10.1093/eurheartj/ehr254. PubMed PMID: 21821849.

37. Georgiadis D, Sievert M, Cencetti S, Uhlmann F, Krivokuca M, Zierz S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. Eur Heart J. 2000;21(5):407-13. Epub 2000/02/10. doi: 10.1053/euhj.1999.1742. PubMed PMID: 10666355.

38. Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc. 2009;57(11):2029-36. Epub 2009/09/17. doi: 10.1111/j.1532-5415.2009.02485.x. PubMed PMID: 19754498.

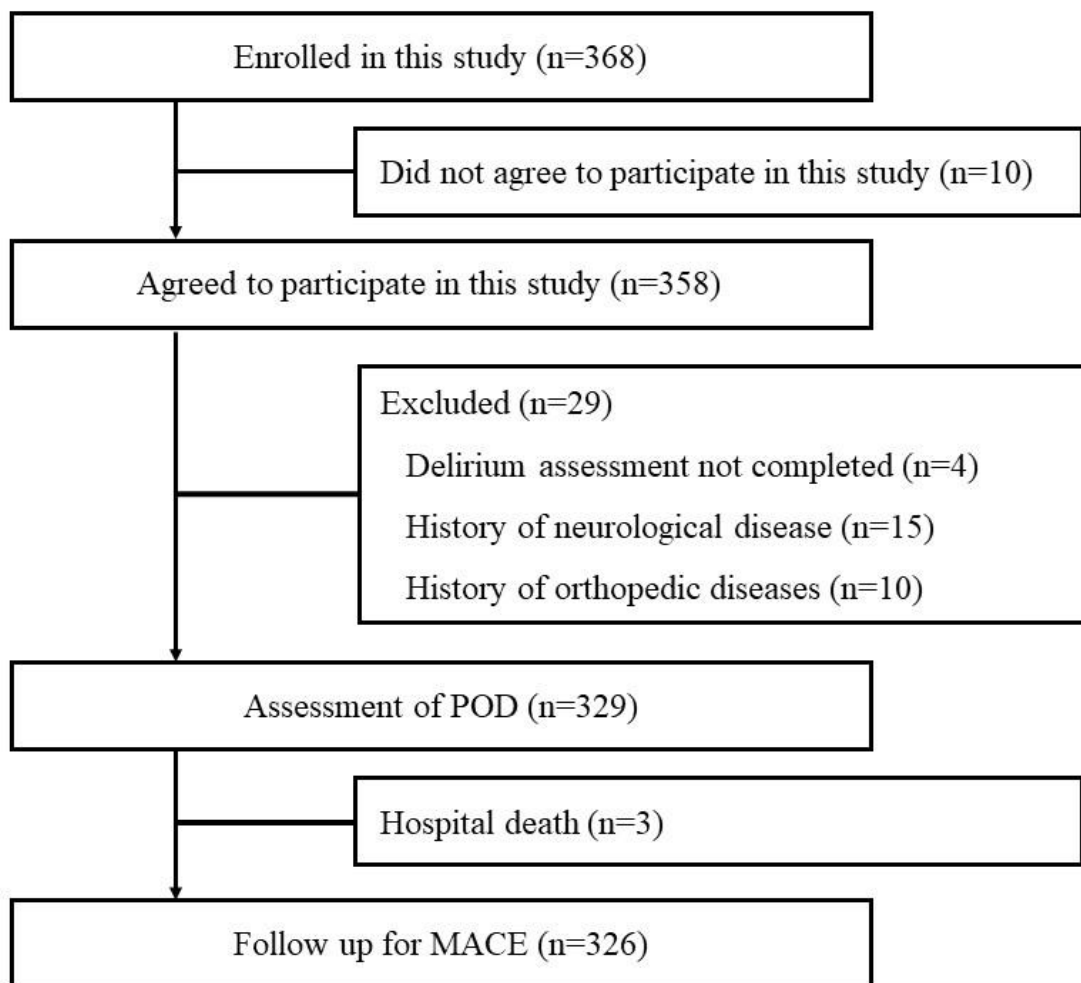
## Figure legends

**Fig. 1.** The flow chart displays the patient flow during the study.

POD, postoperative delirium; MACE, major adverse cardiac events

**Fig. 2.** Kaplan-Meier curves for cumulative major adverse cardiac events for (A) presence (red line) or absence (black line) of postoperative delirium (Log-rank test,  $p=0.000733$ ), (B) a comparison of the four groups robust (blue line), delirium (black line), postoperative frailty (red line), and combination of both (green line) (Log-rank test,  $p=0.00369$ ).

Figure. 1





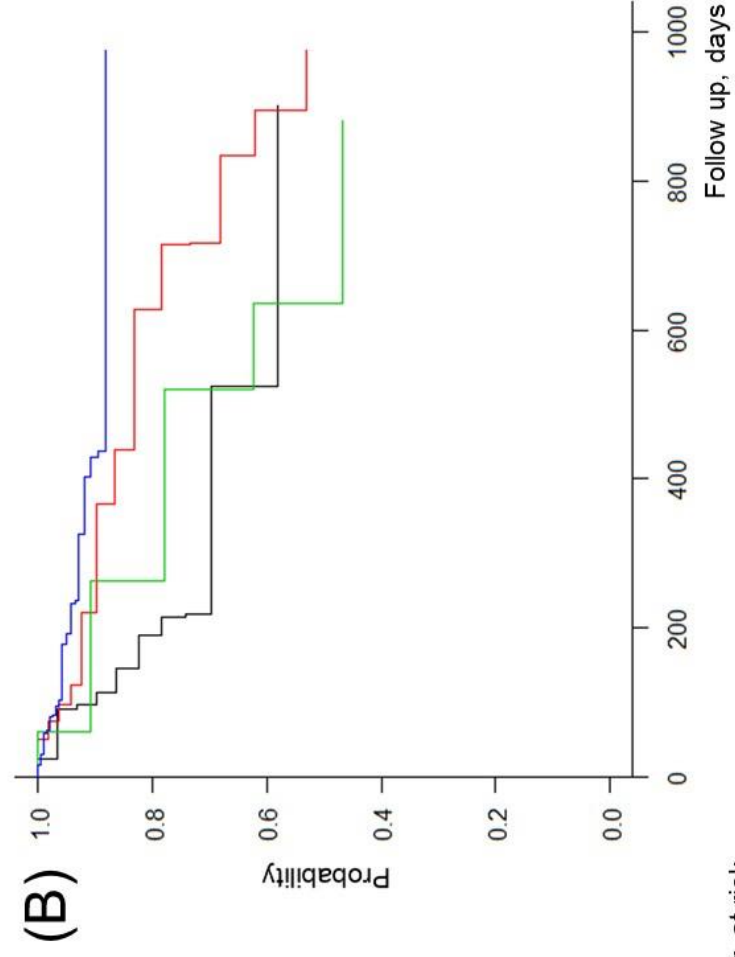
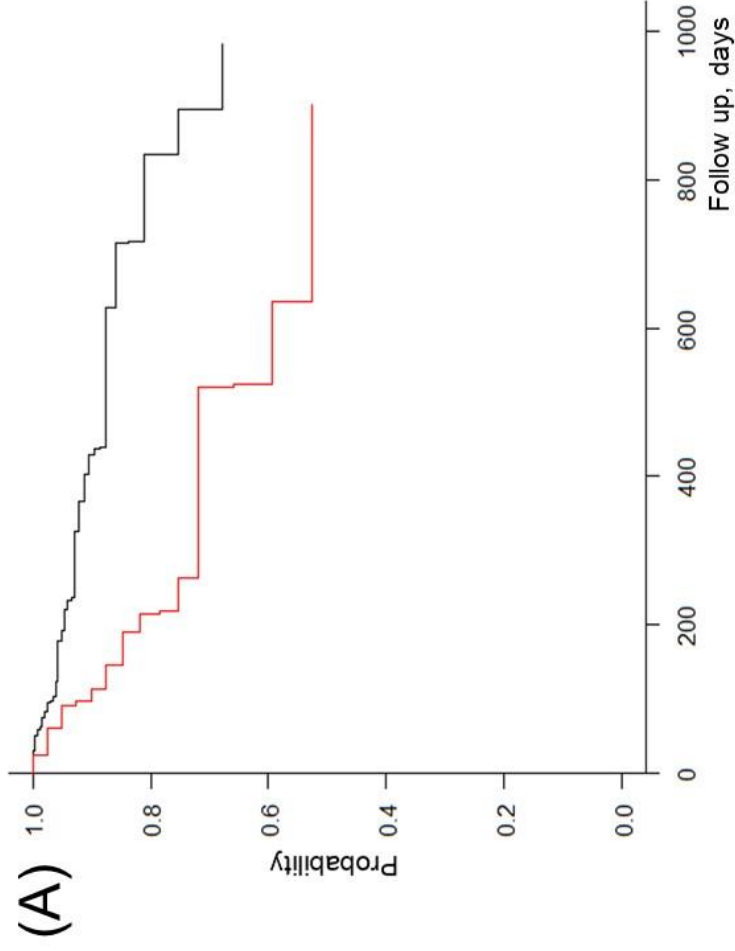


Figure. 2