Acute Limb Ischemia after Cardiovascular Surgery: A Deadly Duo Combination with High Mortality

Suci Indriani, MD[1] Raditya Dewangga, MD[2] Suko Adiarto, MD, PhD, FICA[1] Taofan Siddiq, MD, FICA[1] Iwan Dakota, MD, PhD, FICA[1] Hananto Andriantoro, MD, PhD, FICA[1] Marc Vuylsteke, MD, PhD[3]

[1] Department of Cardiology and Vascular Medicine, Universitas Indonesia/Harapan Kita National Cardiovascular Center, Jakarta, Indonesia
[2] Department of Emergency Medicine, Gunung Jati General Hospital, Cirebon, Indonesia
[3] Department of Vascular Surgery, Sint-Andriesziekenhuis, Tielt, Belgium

Address for correspondence Suci Indriani, MD, Department of Cardiology and Vascular Medicine, Universitas Indonesia/Harapan Kita National Cardiovascular Center, Jl. Letjend S Parman kav. 87, Slipi, 11420, Jakarta, Indonesia (e-mail: suci_fkui02@yahoo.com).

Int J Angiol 2023;32:158–164.

Abstract

Acute limb ischemia (ALI) is a predictor of high morbidity and mortality. Previous studies showed that ALI developed after cardiac surgery may increase mortality.

This study aimed to elucidate the clinical course and identify risk factors contributing to mortality in patients with ALI after cardiovascular surgery.

This is a single-center retrospective cohort study. We analyzed data from 52 patients with ALI after cardiovascular surgery between 2016 and 2020. We evaluated the risk factors for 1-year mortality using Cox proportional hazards regression analysis.

Most of the patients with ALI were male and the median age was 56 years (23–72 years). Most of the patients with ALI had coronary artery diseases. The 1-year mortality rate was 55.8% ($n = 29$ patients). Multivariable analysis revealed that cardiopulmonary bypass (CPB) time $\geq$ 100 minutes (hazard ratio [HR]: 3.067, 95% confidence interval [CI]: 1.158–8.120) and postoperative acute kidney injury (HR: 2.927, 95% CI: 1.358–6.305) were significantly increasing the risk of mortality in patients with ALI after an operation. ALI after cardiovascular surgery was associated with high 1-year mortality in our study and long CPB time and postoperative acute kidney injury contributed to the mortality.

Keywords
- acute limb ischemia
- cardiovascular surgery
- mortality

Acute limb ischemia (ALI) is one of the potentially life-threatening events in vascular disease. The incidence of ALI is approximately 1.5 cases per 10,000 persons per year.[1] Thirty-day mortality and amputation rates in ALI are 15 and 25%, respectively.[2] Data from our hospital showed that the intrahospital and 30-day mortality rates from ALI are 28.1 and 36.9%, respectively.[3]

When ALI developed after cardiac surgery, the mortality rate was higher and reached 45% in two separate cohorts.[4,5] Folkert et al found that ALI after cardiac surgery was only 1.4%, but it was associated with a significant risk for amputation and reduced long-term survival. The risk factors for developing ALI after open cardiac surgery were extracorporeal membrane oxygenation (ECMO) support, emergency operative status, intra-aortic balloon pump (IABP), heart transplant, peripheral artery disease, current smoking status, and body mass index. The mortality rate has been reported as 28 to 80% in patients with ECMO and IABP support.[6]

article published online
February 13, 2023

DOI https://doi.org/10.1055/s-0043-1761290.
ISSN 1061-1711.

Meanwhile, there are currently no data on the incidence of ALI after cardiovascular surgery in our national cardiovascular center. This study aimed to identify risk factors contributing to mortality in patients with ALI after cardiovascular surgery.

Material and Methods

Study Design and Data Collection

This study was a retrospective cohort analysis. We analyzed all patients with ALI after cardiovascular surgery between January 1, 2016 and December 31, 2020. These patients were followed for at least 1 year. This study assessed the mortality rate as well as risk factors of 1-year mortality in patients with ALI. This study has been approved by the Harapan Kita National Cardiovascular Center institutional review board (LB.02.01/ VII / 510 / KEP 007 / 2021). This study complies with the Declaration of Helsinki and the Nuremberg Code.

Patient Population

All adult patients who developed ALI following open cardiac or thoracic aortic surgery were enrolled in our study. Patients treated with subsequent structural cardiac intervention in the catheterization lab were excluded. ALI after cardiovascular surgery was defined as any ischemic event in the arterial system of the upper or lower limbs after a surgical procedure in the same index hospitalization.

Statistical Analysis

Data on the baseline characteristics of the subjects were described in the tables. Normally distributed continuous variables were expressed with mean and standard deviation and compared using independent group *t*-tests. In contrast, the nonnormally distributed variables were expressed using median and minimum-maximum values and compared using the Mann–Whitney test. Categorical variables were expressed with frequency and percentages and compared using chi-square or Fisher's exact test. Survival analyses were analyzed using Kaplan–Meier estimates. Variables with a *p*-value of < 0.25 in univariate analysis fulfilling proportional hazard assumption were included in Cox proportional hazards regression multivariate analysis to assess the effect of several risk factors on survival time simultaneously. Selection of variables for retention was based on $p < 0.05$. We considered a two-sided *p*-value of < 0.05 as statistically significant. All analyses were conducted using IBM Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM, New York, NY).

Results

A total of 7,866 patients underwent cardiac surgery from 2016 to 2020. Five patients were excluded because the incidence of ALI did not occur simultaneously with the surgery or because there were concomitant cardiac catheterization procedures, such as balloon mitral valvuloplasty, balloon aortic valvuloplasty, and balloon pulmonary valvulotomy. There were 52 patients (0.66%) who developed ALI after surgery that met the criteria (►**Fig. 1**). Overall mortality was 55.8% ($n = 29$), of which 44.2% ($n = 23$) were still alive 1 year after the surgery. Baseline characteristics of our population are shown in ►**Table 1**.

Most of the patients with ALI were male (57.7%), and the median age was 56 years (23–72 years). Note that 65.4% of patients with ALI had coronary artery diseases. The median onset of ALI after the surgery was 24 hours (0.5–288 hours). The proportion of patients with stage IIB or III (Rutherford

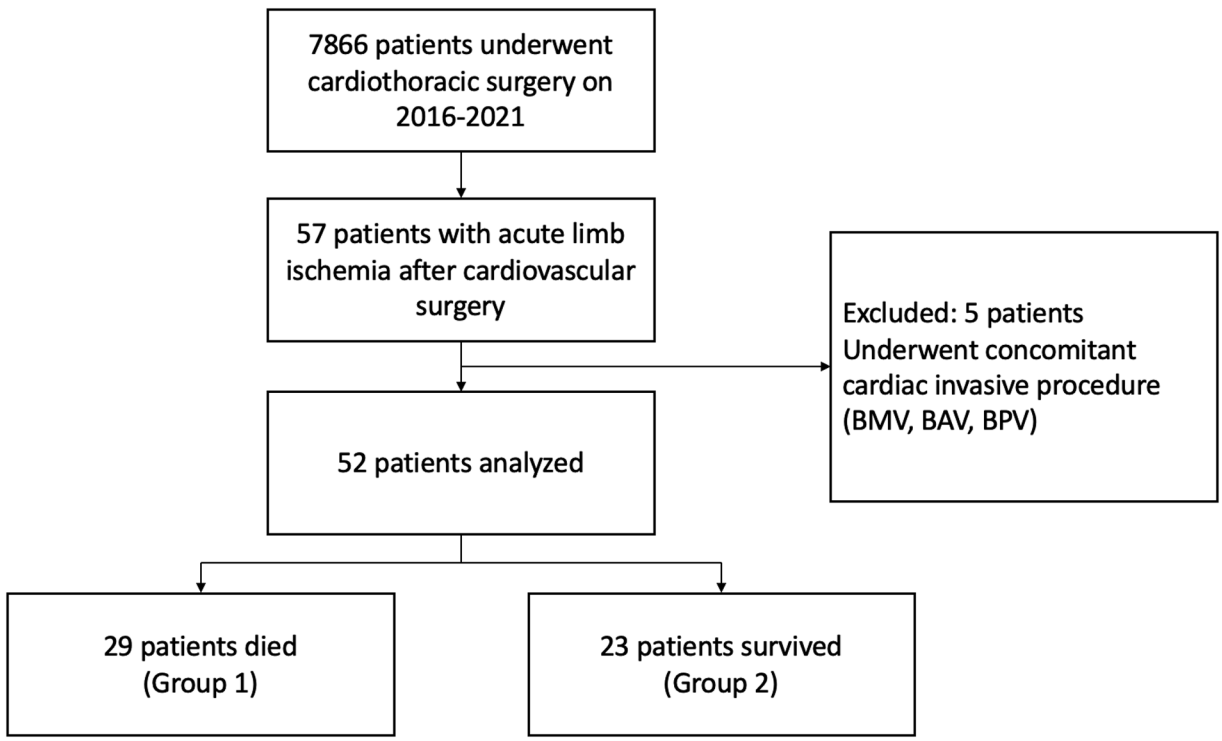

Fig. 1 Flowchart of patients included and excluded in the study.

Table 1 Baseline characteristics of population study

Parameters	*n* (%)	Mortality		*p*-Value
		Yes ($n = 29$)	No ($n = 23$)	
Age, y	56 (23–72)	59 (23–72)	47 (33–71)	0.067
Male	30 (57.7)	19 (63.3)	11 (36.7)	0.200
Smoking history	17 (32.7)	12 (70.6)	5 (29.4)	0.134
Concomitant disease				
Hypertension	32 (61.5)	18 (56.3)	14 (43.8)	0.930
Diabetes mellitus	10 (19.2)	8 (80)	2 (20)	0.155
Dyslipidemia	10 (19.2)	5 (50)	5 (50)	0.734
Coronary artery disease	34 (65.4)	22 (64.7)	12 (35.3)	0.075
Valvular disease	13 (25)	6 (46.7)	7 (53.8)	0.420
Aortic dissection	5 (9.6)	3 (60)	2 (40)	1.000
Peripheral artery disease	4 (7.7)	2 (50)	2 (50)	1.000
Atrial fibrillation	9 (17.3)	6 (66.7)	3 (33.3)	0.714
Onset, h	24 (0.5–288)	24 (1–168)	36 (0.5–288)	0.647
ALI stage I and IIA	29 (55.8)	16 (55.2)	13 (44.8)	0.922
ALI stage IIb and III	23 (44.2)	13 (56.5)	10 (43.5)	
Location of occlusion				
Upper extremity	2 (3.8)	2 (100)	0	0.497
Iliofemoral	28 (53.8)	15 (53.6)	13 (46.4)	0.730
Popliteal-tibial	29 (55.8)	19 (65.5)	10 (34.5)	0.112
Dorsal pedis-digital	13 (25)	8 (61.5)	5 (38.5)	0.629
Embolic cause	20 (38.5)	12 (60)	8 (40)	0.627
Surgical parameter				
Urgent or emergency	26 (50)	14 (53.8)	12 (46.2)	0.780
CABG surgery	30 (57.7)	22 (73.3)	8 (26.7)	0.003
Valve surgery	15 (28.8)	6 (40)	9 (60)	0.145
Aortic surgery	7 (13.6)	4 (57.1)	3 (42.9)	1.000
Cardiopulmonary bypass time $\geq$ 100 min	34 (65.4)	24 (70.6)	10 (29.4)	0.003
Aortic cross clamp time $>$ 60 min	35 (67.3)	21 (60)	14 (40)	0.378
Intra-aortic balloon pump insertion	28 (53.8)	17 (60.7)	11 (39.3)	0.438
Supporting examination				
Ejection fraction $<$ 40%	16 (30.8)	10 (62.5)	6 (37.5)	0.468
Hemoglobin, g/dL	12.2 ± 2.5	12.4 ± 2.7	12.0 ± 2.3	0.597
Leukocyte, /mm^3	11810 (4270–40540)	11615 (5340–40540)	10100 (4270–29520)	0.985
Platelet, /mm^3	262978 ± 115125	243200 ± 85367	287915 ± 118000	0.318
Fibrinogen, mg/dL	390 (230–709)	363 (230–493)	394 (243–709)	0.465
eGFR, mL/min/1.73 m^2	61.7 ± 22.0	57.5 ± 26.4	66.9 ± 33.8	0.347
D-dimer, mg/dL	1761 (487–15733)	1800 (1344–5227)	1722 (487–15733)	0.808
Postoperative complications				
Sepsis	13 (25)	9 (69.2)	4 (30.8)	0.259
Cerebrovascular event	2 (3.8)	1 (100)	1 (100)	1.000
Gastrointestinal bleeding	11 (21.2)	9 (81.8)	2 (18.2)	0.086
Acute kidney injury	22 (42.3)	18 (81.8)	4 (18.2)	0.001

Table 1 (*Continued*)

Parameters	*n* (%)	Mortality		*p*-Value
		Yes (*n* = 29)	No (*n* = 23)	
Hospital length of stay (d)	15 (2-54)	11 (2-40)	24 (8-54)	<0.001
ICU length of stay (d)	5 (1-39)	5 (1-39)	5 (1-32)	0.573
Amputation rate	4 (7.7)	1 (25)	3 (75)	0.310

Abbreviations: ALI, acute limb ischemia; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

classification) in the deceased group tended to be higher than in the survivor group (56.5% vs. 43.5%). From the duplex ultrasound examination, the incidence of acute ischemia of the upper extremity was rare (3.8%). However, the iliac-femoral, popliteal-tibial, and dorsal pedis-digital arteries were commonly involved with the percentage of 53.8, 55.8, and 25%, respectively.

Fifty percent of patients identified with ALI were patients who underwent emergency surgery. Coronary artery bypass graft (CABG) surgery was the predominant procedure in deceased patients compared to the survivor patient (73.3%). An IABP support was inserted mostly in the deceased group (60.7%). Cardiopulmonary bypass (CPB) time was significantly longer (159.7 ± 52.9 vs. 102.7 ± 51.16 minutes, *p*: 0.014) and aortic cross-clamp times were also longer in the deceased group. Only 16 patients (30.8%) with ALI had a low ejection fraction.

Most patients with ALI experienced significant postoperative complications, including sepsis (25%), gastrointestinal bleeding (21.2%), cerebrovascular disease (3.8%), and acute kidney injury (AKI) (42.3%). The AKI was significantly higher in the deceased group than in the survivor group (81.8% vs. 18.2%). The median length of stay in the intensive care unit (ICU) and hospital was 5 and 15 days, respectively.

A multivariable model was developed to assess factors associated with 1-year mortality in the patients using Cox regression analysis (►**Table 2**). CPB time $\geq$ 100 minutes and postoperative AKI were significantly increasing the risk of mortality in patients with ALI after an operation with hazard ratio (HR) of 3.067 (95% confidence interval [CI] 1.158–8.120) and HR 2.927 (95% CI 1.358–6.305), respectively. Kaplan–Meier curve is shown in ►**Figs. 2** and **3**.

Patients who developed ALI after cardiovascular surgery had a high short-term mortality rate. In our study, 28 patients died while still in the hospital, and only one patient died after discharge.

Discussion

In this study, the prevalence of ALI after the cardiovascular operation was very low at 0.66%, but with very high mortality events (55.8%). In a previous study by Allen et al a similar incidence of ALI after cardiovascular surgery was found (0.85%).[4] This number was significantly lower than the results presented in a study by Folkert et al, who found the incidence of ALI to be 1.4% during 10 years of observation.[6]

Most patients who develop ALI after cardiovascular surgery have a higher short-term risk of death, as death within 30 days of surgery. After that, the risk was the same.[6] This is consistent with our findings that 25 patients died in the hospital during the postoperative period. Only one patient died 6 months after discharge from the hospital. The critical time for survival in ALI patients was in the acute phase, especially during the index hospitalization.

One-year mortality of ALI after cardiovascular surgery in our center was 56.5%. Our mortality rate is higher than the

Table 2 Factors associated with 1-year mortality in patients with postoperative acute limb ischemia in Cox regression analysis

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age > 60	1.637	0.789–3.396	0.185			
Male	1.536	0.712–3.316	0.274			
Smoker	1.785	0.847–3.761	0.128			
Diabetes mellitus	1.763	0.774–4.012	0.177			
Coronary artery disease	2.002	0.853–4.699	0.111			
CABG surgery	3.192	1.355–7.519	0.008			
Valve surgery	0.523	0.212–1.290	0.160			
Cardiopulmonary bypass time $\geq$ 100 min	3.587	1.364–9.427	0.010	3.067	1.158–8.120	0.024
Postoperative GI bleeding	1.985	0.901–4.375	0.089			
Postoperative acute kidney injury	3.359	1.567–7.200	0.002	2.927	1.358–6.305	0.006

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio.

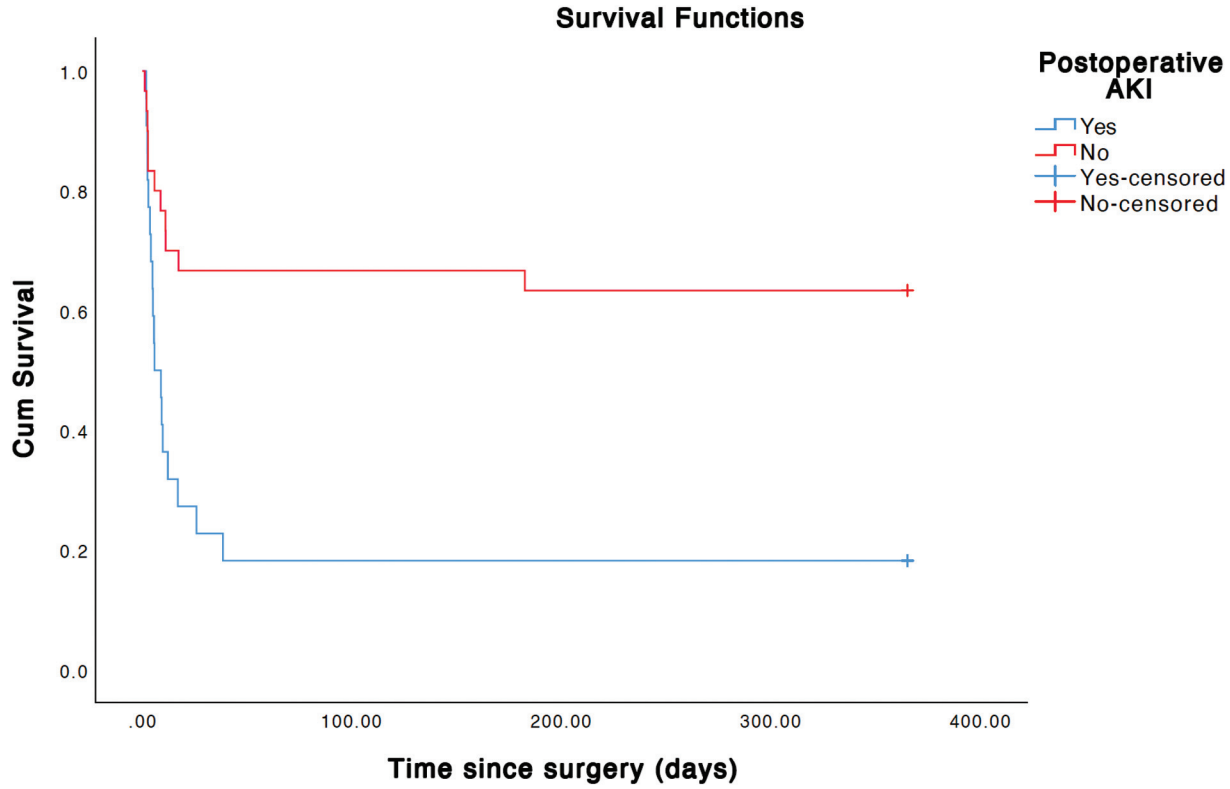

Fig. 2 Comparison of survival between acute kidney injury (AKI) and non-AKI patients.

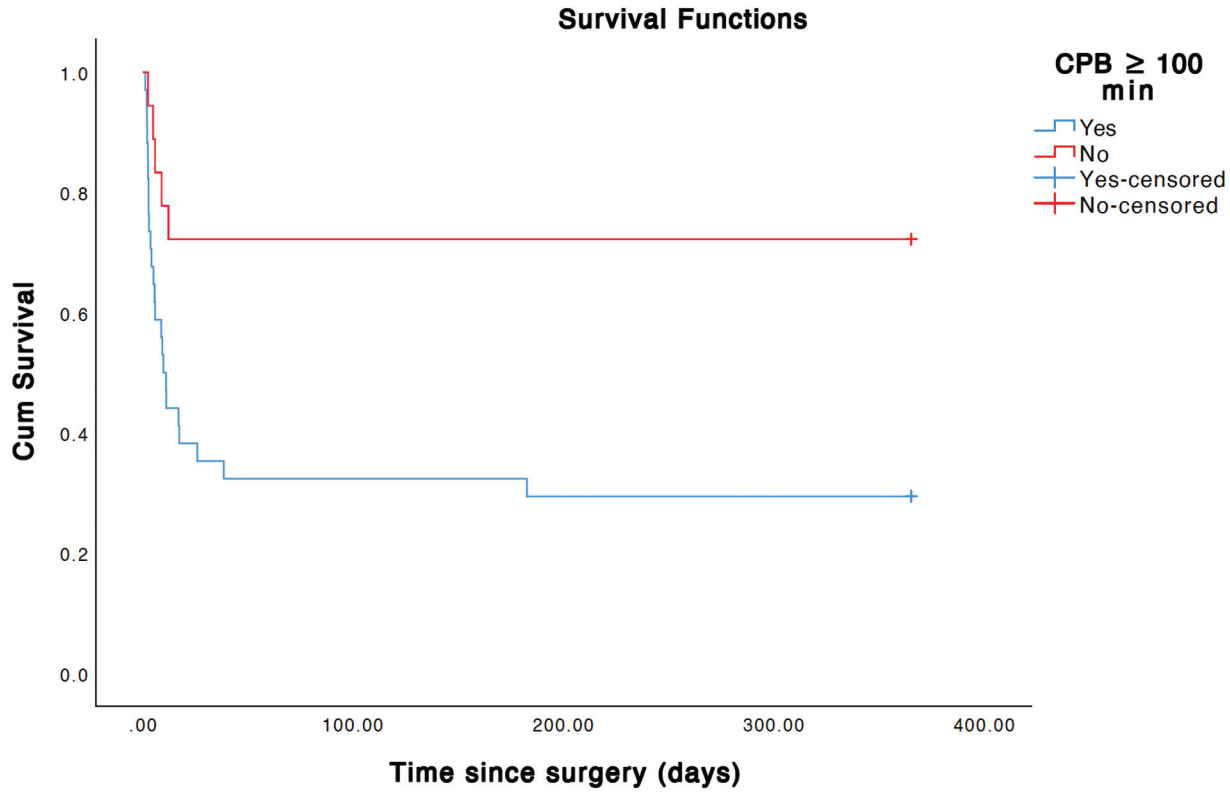

Fig. 3 Comparison of survival between patients with cardiopulmonary bypass time $\geq$ 100 minutes versus $<$ 100 minutes.

previous study by Allen et al and Folkert et al. The mortality rates in their study were nearly very similar at about 46 and 45%, respectively.[4,6]

There are several possibilities of the cause of the high mortality rate. First, there was higher comorbidity in the patients. Patients from the deceased group tend to be older and have more coronary artery disease, atrial fibrillation, hypertension, and renal dysfunction. This reflects diffuse and multivessel disease involving the coronary and peripheral vasculature. The fact that overall mortality rates of acute ischemia have not improved dramatically over the past 20 years no doubt reflects the severity of the underlying diseases in these high-risk patients.[7] Second, regarding the surgical procedure in patients from the deceased group had a higher proportion of CABG operations and long CPB and aortic cross-clamp time compared to the survivor group. Any coronary bypass operation with a long CPB time is associated with a higher risk of developing ALI after cardiac surgery.[6] Mesh et al found that patients with vascular disease required longer cross-clamp times (63.1 ± 25.3 minutes) and CPB time ($> 108.3 \pm 42.2$ minutes).[8] The longer the lower extremities are not perfused, the more susceptible they become ischemic and thus increase the morbidity and mortality rate.[5]

Regarding the limb loss, of the patients represented with ALI after cardiovascular surgery, four patients (7.7%) required amputations during the index hospitalization, but only three were amputated. One patient did not undergo amputation because the patient did not survive. Folkert et al also showed that the rate of amputation was 9.8% in their study.[6] When patients survived and were discharged, the mortality rate from limb loss rate was significantly reduced. Zero mortality and amputation occurred after 6-month to 1-year follow-up in our research.

Using multivariate Cox regression analysis, we identified two factors associated with 1-year mortality in ALI patients after cardiovascular surgery. CPB time $\geq$ 100 minutes and postoperative AKI were significantly increasing the risk of mortality in patients with ALI after an operation with HR 3.067 (95% CI 1.158–8.120) and HR 2.927 (95% CI 1.358–6.305), respectively.

Regarding CPB time, every minute counts. Ng et al showed that prolonged bypass time ($\geq$ 100 minutes) was associated with mortality.[9] Madhavan et al found that prolonged CPB time ($>$ 180 minutes) in CABG patients significantly predicted mortality after adjusting with EuroSCORE II, postoperative complications, prolonged ICU stay, and prolonged mechanical ventilation.[10]

AKI is defined as a deterioration of kidney function over hours or days following surgery, with symptoms including oliguria (urine output less than 400 mL/day), parallel rises in serum blood urea nitrogen, and creatinine, and the development of severe electrolyte and acid-base disorders.[11] Cardiovascular surgery itself can contribute to AKI development and is implicated as a contributing factor in elevated mortality and poor outcome.[12,13] The pathogenesis of AKI after cardiac surgery is multifactorial, complex, and incompletely understood. Several injury pathways contribute to the development of AKI after cardiovascular surgery: a combination of hemodynamic instability, mechanical stress such as CPB, inflammation, oxidative stress, neurohormonal factors, nephrotoxic agents, and postoperative complications such as infections and ischemic-reperfusion injury.[14,15] In ALI, ischemic-reperfusion injury plays a pivotal role. Early death in ALI is mainly caused by metabolic disorders associated with reperfusion syndrome following revascularization.[16] Reperfusion of rhabdomyolytic muscle induces the release of myoglobin, a potential renal toxin causing acute tubular necrosis. Reperfusion also induces an overflow of intracellular potassium and hydrogen ions due to the destroyed potassium-sodium pump causing metabolic acidosis and fatal arrhythmia.[17] A combination of AKI after cardiovascular surgery and ALI is therefore very lethal and was one of the predictors of death in our study. Allen et al also reported that one of the causes of death in ALI postcardiac surgery was renal failure.[4]

Limitation

All the data were collected retrospectively from the medical record in which some of the patients' data were incomplete and lost during the follow-up. More subjects and a bigger sample are needed to gain a more confident result.

Conclusion

ALI is a rare but severe complication after cardiovascular surgery associated with increased morbidity and 1-year mortality. One-year mortality from ALI after cardiovascular surgery in our center was very high at 55.8%. Two factors associated with the 1-year mortality of ALI patients after cardiovascular surgery in our study are CPB time $\geq$ 100 minutes and AKI after surgery.

Conflict of Interest
None declared.

References

1 Norgren L, Hiatt WR, Dormandy JA, et al; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(suppl 1): S1–S75
2 Rajan DK, Patel NH, Valji K, et al; CIRSE and SIR Standards of Practice Committees. Quality improvement guidelines for percutaneous management of acute limb ischemia. J Vasc Interv Radiol 2009;20(07, suppl):S208–S218
3 Indriani S, Adiarto S, Andriantoro H, Sunu I, Siddiq T, Dakota I. The protective effect of vitamin E for reducing intra-hospital mortality in acute limb ischemia patients. Indones J Cardiol 2021;42:4
4 Allen RC, Schneider J, Longenecker L, Kosinski AS, Smith RB III, Lumsden AB. Acute lower extremity ischemia after cardiac surgery. Am J Surg 1993;166(02):124–129, discussion 129
5 Kohlman-Trigoboff D, Gongora E, Stanford J, Smith BM. Risk factors associated with acute lower extremity ischemia after coronary revascularization. J Vasc Nurs 2002;20(03):78–83
6 Folkert IW, Foley PJ, Wang GJ, et al. Impact of acute postoperative limb ischemia after cardiac and thoracic aortic surgery. J Vasc Surg 2018;67(05):1530–1536.e2

7 Dormandy J, Heeck L, Vig S. Acute limb ischemia. Semin Vasc Surg 1999;12(02):148–153
8 Mesh CL, Cmolik BL, Van Heekeren DW, et al. Coronary bypass in vascular patients: a relatively high-risk procedure. Ann Vasc Surg 1997;11(06):612–619
9 Ng WK, Vedder M, Whitlock RML, et al. Coronary revascularisation in young adults. Eur J Cardiothorac Surg 1997;11(04):732–738
10 Madhavan S, Chan S-P, Tan W-C, et al. Cardiopulmonary bypass time: every minute counts. J Cardiovasc Surg (Torino) 2018;59 (02):274–281
11 Olivero JJ, Olivero JJ, Nguyen PT, Kagan A. Acute kidney injury after cardiovascular surgery: an overview. Methodist DeBakey Cardiovasc J 2012;8(03):31–36
12 Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15(06):1597–1605
13 Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol 2005;16(01):195–200
14 Chew STH, Hwang NC. Acute kidney injury after cardiac surgery: a narrative review of the literature. J Cardiothorac Vasc Anesth 2019;33(04):1122–1138
15 Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol 2017;13(11):697–711
16 Kazimierczak A, Szumiłowicz P, Samad R, et al. Kidney protection therapy in acute limb ischemia [in Polish]. Ann Acad Med Stetin 2013;59(02):7–11
17 Fukuda I, Chiyoya M, Taniguchi S, Fukuda W. Acute limb ischemia: contemporary approach. Gen Thorac Cardiovasc Surg 2015;63 (10):540–548