Original Article

Risk factor and correlation between postoperative serum myoglobin and acute kidney injury after pulmonary endarterectomy

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Background: Acute kidney injury (AKI) is a common and life-threatening complication following pulmonary endarterectomy (PEA). Our study aimed to investigate the risk factors associated with AKI and evaluate the correlation between serum myoglobin (sMb) levels and postoperative AKI.

Methods: We conducted a retrospective study involving 134 patients who underwent PEA at China-Japan Friendship Hospital. AKI was defined and staged according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Results: During the study period, the incidence of postoperative AKI was 57.5%, and the associated mortality rate was 6.0%. Severe AKI was found to be significantly associated with worse short-term outcomes (P<0.05). Logarithmically transformed postoperative day (POD) 0 sMb levels were significantly associated with AKI [odds ratio (OR) =5.174; 95% confidence interval (CI), 2.307–11.603; P<0.001] and severe AKI (OR =4.605; 95% CI, 1.510–14.048; P=0.007), also had independent predictive value [area under the curve (AUC) =0.776 in AKI and AUC =0.737 in severe AKI]. The optimal cut-off values were 370.544 ng/mL for AKI and 419.473 ng/mL for severe AKI. Furthermore, albumin concentration was found to play a protective role in the development of severe AKI (OR =0.838; 95% CI, 0.716–0.980; P=0.027) when higher than 40.350 g/L.

Conclusions: Our findings suggest that a high concentration of POD0 sMb may increase the risk of developing AKI following PEA surgery. Increasing albumin concentration could serve as an effective preventive measure against AKI.

Keywords: Acute kidney injury (AKI); myoglobin; pulmonary endarterectomy (PEA)

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complex and progressive pulmonary vascular disease characterized by the obstruction of pulmonary arteries with unresolved thrombofibrotic material (1). Patients commonly present with symptoms such as dyspnea, chest pain, and pulmonary arterial hypertension (PAH), which can eventually lead to right heart failure over the course of the disease (2). Pulmonary endarterectomy (PEA) is recommended as the gold standard curative treatment for operable CTEPH patients (3,4). Following cardiothoracic surgery (CAS) performed on cardiopulmonary bypass (CPB), acute kidney injury (AKI) is a relatively common postoperative complication that is associated with prolonged intensive care unit (ICU) stay and increased mortality (5,6). Early identification and diagnosis of postoperative AKI are crucial for optimal patient management and improved outcomes (7). The reported incidence of AKI after PEA ranges from 26.5% to 45.0% (8,9). Although the underlying mechanisms of CAS-AKI are multifactorial and largely unknown, several pathophysiologic processes have been reported (10). Myoglobin, a small protein (19 kD) and a commonly measured biomarker, is produced due to surgery-associated myocardial and skeletal muscle rupture, leading to its release into circulation. This can cause toxic effects and damage renal proximal tubular cells (11,12). The correlation between perioperative serum myoglobin (sMb) levels and AKI has been reported in various surgical procedures (13-15). However, the relevance and strength of sMb in relation to AKI following PEA have not been demonstrated. In this study, we aim to explore the risk factors and assess the correlation between sMb levels and the occurrence of postoperative AKI. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1510/rc).

Highlight box

Key findings

- Increasing albumin concentration may be an effective preventive measure for acute kidney injury (AKI), and elevated postoperative day 0 serum myoglobin (sMb) concentration increases the risk of AKI after pulmonary endarterectomy (PEA).

What is known and what is new?

- The correlation between perioperative sMb levels and AKI has been reported in various surgical procedures, However, the relevance and strength of sMb in relation to AKI following PEA have not been demonstrated.
- In addition to explore the risk factors of AKI after PEA, we also assessed the correlation between sMb levels and the occurrence of postoperative AKI.

What is the implication, and what should change now?

- Focusing on myoglobin levels may help clinicians identify patients at risk of AKI and enable timely intervention to improve patient prognosis.

Methods

Study population

The study included a cohort of 138 consecutive patients with CTEPH who underwent PEA at China-Japan Friendship Hospital between December 2016 and September 2023. Patients were excluded if they were under 18 years old, had end-stage renal disease (ESRD) requiring preoperative dialysis, or died within 7 days after surgery. Ultimately, 134 individuals were enrolled in the study (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-088) and the requirement for individual consent for this retrospective analysis was waived.

Surgical procedure

The surgical procedure was performed as previously described (16). The standard approach for PEA involved a median sternotomy under general anesthesia to ensure optimal visualization of bilateral PEA. After longitudinal pericardiotomy, CPB was established using high ascending aortic cannulation and two caval cannulae. The surgery was carried out under deep hypothermic circulatory arrest (DHCA). Once the core temperature reached 20 ℃, circulation was stopped by clamping the ascending aortic artery. Repeated periods of DHCA limited to 20 minutes were performed with re-establishment of CPB in between. The obstructive material was dissected using a suction dissector placed between the material and the artery wall. Rewarming was initiated after completion of endarterectomy and pulmonary artery anastomosis on both sides. When the core temperature reached 36 ℃, the patient was weaned from CPB. After the procedure, the patient was transferred to the ICU for further treatment.

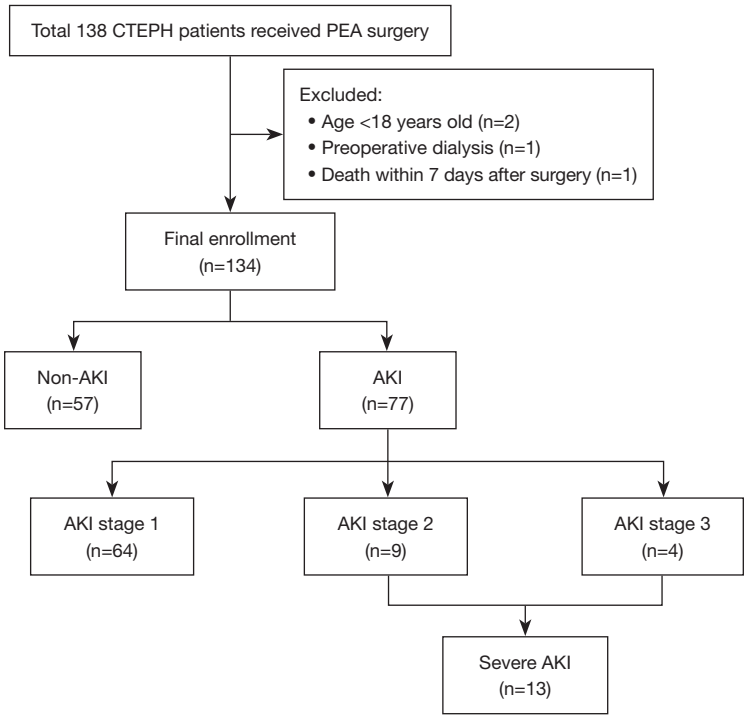

Figure 1 Flow diagram of the CTEPH patients undergoing PEA surgery. CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; AKI, acute kidney injury.

Data collection and definition

Clinical data, including demographic characteristics, comorbidities, laboratory tests, preoperative transthoracic echocardiography (TTE), features from right heart catheterization (RHC), intraoperative details and outcomes, were retrospectively collected from the electronic medical record system of China-Japan Friendship Hospital. The preoperative baseline serum creatinine (pre-sCr) was defined as the mean outpatient concentration measured one month before hospitalization (17). The preoperative estimated glomerular filtration rate (pre-eGFR) was calculated using the creatinine-based CKD epidemiology collaboration (CKD-EPI) equation in adults (18). Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), mineralocorticoid receptor antagonist (MRA), diuretics and antibiotic use was defined as the occurrence from hospital admission until the day of surgery, as well as exposure to contrast medium within the three days preceding surgery. Serum creatinine (sCr) were collected for 8 consecutive days. Specifically, sCr was collected on postoperative days (PODs) 0 to 7, with each measurement denoted as POD[n]-sCr where [n] indicates day number (i.e., POD0-sCr, POD1-sCr, POD2-sCr, etc.). Additionally, sMb values were collected for 5 consecutive days, beginning with preoperative baseline sMb (pre-sMb) and then PODs 0 to 3, with each measurement denoted as POD[n]-sMb where [n] indicates day number (i.e., POD0-sMb, POD1-sMb, POD2-sMb, etc.). The mean pulmonary artery pressure (mPAP) ≥25 mmHg and pulmonary capillary wedged pressure (PCWP) ≤15 mmHg measured by RHC 24 hours post-PEA was defined as residual pulmonary hypertension (RPH). University of California, San Diego (UCSD) classification of PFA disease levels was used to categorize surgical specimens (16).

Endpoint events and related definitions

AKI was defined and staged according to the criteria established by the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (19,20). Postoperative AKI was classified based on the sCr levels. Stage 1 was defined as an increase of ≥0.3 mg/dL (26.5 μmol/L) within 48 hours after surgery or an increase of 1.5- to 1.9-fold over baseline within 7 days. Stage 2 was

defined as an increase of 2.0- to 2.9-fold over baseline, and stage 3 was defined as an increase of 3.0-fold over baseline, an increase of ≥4.0 mg/dL (353.6 μmol/L), or the initiation of renal replacement therapy. Due to unreliable records, urine output was not included as a criterion for AKI classification. The primary outcomes of the study were AKI (KDIGO stage 1 or higher) and severe AKI (KDIGO stage 2 and 3). The secondary outcomes included 30-day operative mortality, which was defined as death within 30 days after surgery. Other short-term secondary outcomes included the occurrence rate of extracorporeal membrane oxygenation (ECMO), tracheotomy, mechanical ventilation time (MVT), length of intensive care unit stay (LOIS), and postoperative length of hospital stay (p-LOHS).

Statistical analysis

Continuous variables are presented as mean ± standard deviation for normally distributed data or median (25th, 75th percentile) for non-normally distributed data. Categorical variables are reported as frequencies (percentages). Student's *t*-test was used for normally distributed continuous variables, while the Mann-Whitney *U*-test was used for non-normally distributed continuous variables. The chi-square test or Fisher's exact test was used to compare categorical variables among different groups. Variables with a non-linear relationship were converted into dichotomous variables using clinically sensible cut-off points. sCr and sMb values were transformed using the natural logarithm due to their skewed distributions. Pearson rank correlation analysis was performed to determine the linear correlation between Ln(sCr) and Ln(sMb). Univariate logistic regression analysis was used to identify risk factors for AKI, and all variables with a P value <0.05 in the univariate analysis were included in the multivariable model. A stepwise backward method was used for regression analysis, and multicollinearity was assessed using a variance inflation factor (VIF) of <10. The Hosmer-Lemeshow goodness-of-fit statistic was performed to evaluate the fitness of the final model. The results are expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the tested parameters, and cutoff values were determined based on the maximum of Youden's index to calculate the optimum concentration. Delong's test was used to compare the performance of the two ROC curves. Stepwise linear regression analysis was used to assess independent predictors for the Ln(POD0-sMb). Statistical analysis was conducted using SPSS 27.0 (IBM Corp., Chicago, USA) and GraphPad Prism 10.0 (GraphPad Software, Inc., San Diego, CA, USA), and a P value <0.05 (two-sided) was considered statistically significant.

Results

Patient characteristics and postoperative AKI incidence

Table 1 presents the demographic and perioperative clinical characteristics of the 134 patients who underwent PEA. According to the definition of AKI, the incidence of post-PEA AKI was 57.5% (77/134) (*Table 1*). A total of 13 (9.7%) patients with KDIGO stage 2 and 3 were classified as having severe AKI. AKI patients were slightly older and predominantly male compared to non-AKI patients, although the differences were not statistically significant (*Table 1*).

In comparison to non-AKI patients, AKI patients exhibited higher levels of preoperative and postoperative mPAP and PVR. Additionally, AKI patients experienced longer surgery time, CPB time, and ACC time (*Table 1*). Patients who developed severe AKI had lower lymphocyte counts and albumin levels, higher levels of postoperative mPAP and PVR, and longer CPB time and ACC time (*Table 1*, Table S1). Notably, there was no statistical difference in the duration of DHCA between the two comparisons made (*Table 1*).

Outcomes of patients with AKI

A total of 8 individuals died among the enrolled patients (*Table 2*). Patients in the severe AKI group had a higher mortality rate (23.1% *vs.* 7.8%), longer MVT (134.5 *vs.* 63.5 h) and LOIS (15.0 *vs.* 6.0 d). No significant differences were observed in the ECMO utilization, tracheotomy rates and p-LOHS between the two comparisons made (*Table 2*, Table S1).

Perioperative quantitative tendency of sCr and sMb

The baseline levels of pre-sCr and pre-eGFR were 76.0±3.9 μmol/L and 98.1±16.5 mL/min/1.73 m^2, respectively (*Table 1*). The highest recorded sCr level was 115.1 μmol/L. Every patient had an eGFR greater than 60 mL/min/1.73 m^2. The use of nephrotoxic agents such as ACEI/ARB, MRA, diuretics, antibiotics, and contrast

Table 1 Demographics and perioperative clinical characteristics of 134 patients with AKI after PEA

Variables	Full cohort (n=134)	Non-AKI (n=57)	AKI (n=77)	Severe AKI (n=13)
Demographic data				
Age (years)	50.4±13.2	48.9±13.9	51.6±12.5	55.8±12.4
Male (%)	91 (67.9)	36 (63.2)	55 (71.4)	10 (76.9)
BMI (kg/m^2)	24.5±3.3	24.0±3.5	24.8±3.1	24.7±3.0
Blood type				
A	48 (35.8)	18 (31.6)	30 (39.0)	3 (23.1)
AB	18 (13.4)	5 (8.8)	13 (16.9)	2 (15.4)
B	56 (41.8)	29 (50.9)	27 (35.1)	6 (46.2)
O	12 (9.0)	5 (8.8)	7 (9.1)	2 (15.4)
Comorbidities (%)				
Hypertension	35 (26.1)	11 (19.3)	24 (31.2)	4 (30.8)
Type 2 diabetes	8 (6.0)	5 (8.8)	3 (3.9)	1 (7.7)
Hyperlipidemia	46 (34.3)	19 (33.3)	27 (35.1)	4 (30.8)
CAD	10 (7.5)	2 (3.5)	8 (10.4)	2 (15.4)
COPD	28 (20.9)	11 (19.3)	17 (22.1)	4 (30.8)
Laboratory tests				
WBC (×10^9/L)	6.0±1.7	6.2±1.9	5.9±1.5	5.4±1.4
Neutrophil (×10^9/L)	3.7±1.4	3.8±1.5	3.6±1.3	3.5±1.4
Lymphocyte (×10^9/L)	1.7±0.6	1.8±0.6	1.7±0.6	1.3±0.7
Hemoglobin (×10 g/L)	14.2±2.0	14.3±1.9	14.1±2.1	13.5±2.7
Hematocrit (%)	41.3±5.3	41.6±4.9	41.0±5.6	40.4±7.2
Platelet count (×10^9/L)	209.0±66.9	210.4±69.8	208.0±65.1	206.4±73.2
Albumin (g/L)	40.5±3.7	40.1±3.6	40.8±3.8	38.4±3.0
D-dimer >0.5 ng/mL	55 (41.0)	20 (35.1)	35 (45.5)	8 (61.5)
Fibrinogen (g/L)	3.4 (3.0–4.1)	3.5 (2.9–4.1)	3.4 (3.0–4.1)	3.5 (3.2–4.6)
sCr (μmol/L)	76.0±13.9	73.7±15.0	77.8±12.8	77.2±12.5
eGFR (mL/min/1.73 m^2)	98.1±16.5	99.9±17.7	96.8±15.6	95.5±14.2
Pre-sMb (ng/mL)	22.7 (14.7–28.2)	22.3 (14.9–27.5)	22.8 (14.2–29.7)	23.7 (17.1–30.8)
POD0-sMb (ng/mL)	429.9 (303.7–714.6)	317.1 (235.4–415.3)	559.4 (415.5–844.0)	685.8 (482.9–959.5)
POD1-sMb (ng/mL)	335.8 (229.8–527.5)	248.0 (169.2–355.7)	470.5 (293.1–624.3)	604.0 (336.0–885.5)
POD2-sMb (ng/mL)	243.6 (158.8–429.4)	211.1 (134.2–300.4)	305.9 (204.0–471.4)	520.1 (235.5–700.5)
POD3-sMb (ng/mL)	121.0 (72.2–242.7)	91.5 (55.1–142.1)	164.0 (90.1–287.1)	312.0 (136.6–595.9)
Nephrotoxic agents use (%)				
ACEI/ARB	4 (3.0)	2 (3.5)	2 (2.6)	0 (0.0)
MRA	104 (77.6)	41 (71.9)	63 (81.8)	11 (84.6)
Diuretics	116 (86.6)	46 (80.7)	70 (90.9)	13 (100.0)
Antibiotics	13 (9.7)	6 (10.5)	7 (9.1)	2 (15.4)
Contrast media	12 (9.0)	4 (7.0)	8 (10.4)	2 (15.4)

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Full cohort (n=134)	Non-AKI (n=57)	AKI (n=77)	Severe AKI (n=13)
Preoperative TTE				
RV basal diameter (mm)	47.7±8.7	46.5±8.0	48.1±9.1	50.8±8.6
mPA diameter (mm)	33.1±6.0	32.5±6.3	33.5±5.7	36.2±9.2
LVEF (%)	67.2±5.8	67.3±5.1	67.2±6.3	65.2±5.1
Preoperative RHC				
mPAP (mmHg)	41.8±11.9	37.8±11.9	44.7±11.1	45.5±9.5
PVR (dyn·s·cm^{-5}·m^2)	905.1 (593.5–1,120.0)	749.6 (431.0–1,056.3)	960.0 (708.8–1,214.0)	960.0 (736.9–1,334.3)
CI (L/min)	3.2±0.9	3.2±1.0	3.2±0.8	3.3±0.9
Postoperative RHC				
mPAP (mmHg)	22.5±7.9	20.8±7.5	23.8±8.0	26.7±6.8
PVR (dyn·s·cm^{-5}·m^2)	235.1 (151.6–357.4)	193.5 (126.9–284.1)	285.7 (193.3–415.2)	321.6 (225.6–492.4)
RPH (%)	43 (32.1)	15 (26.3)	28 (36.4)	6 (46.2)
Intraoperative transfusion (%)				
PRBCs	32 (23.9)	14 (24.6)	18 (23.4)	5 (38.5)
FFP	45 (33.6)	18 (31.6)	27 (35.1)	5 (38.5)
PLT	13 (9.7)	5 (8.8)	8 (10.4)	3 (23.1)
Intraoperative details				
Surgery time (min)	589.3±77.8	565.9±76.6	606.6±74.6	614.2±50.4
CPB time (min)	346.4±60.1	330.1±66.9	358.5±51.6	379.3±54.7
DHCA duration (min)	60.2±19.0	57.3±21.2	62.3±17.0	63.1±14.4
ACC time (min)	161.6±41.4	149.4±40.5	170.6±40.0	184.9±40.2
Concomitant surgery (%)	17 (12.7)	7 (12.3)	10 (13.0)	3 (23.1)
UCSD classification				
I	80 (59.7)	37 (64.9)	43 (55.8)	9 (69.2)
II	41 (30.6)	15 (26.3)	26 (33.8)	2 (15.4)
III	13 (9.7)	5 (8.8)	8 (10.4)	2 (15.4)

Continuous variables are presented as mean ± standard deviation for normally distributed data or median (25^{th}–75^{th} percentile) for non-normally distributed data. Categorical variables are reported as frequencies (percentages). AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. AKI, acute kidney injury; PEA, pulmonary endarterectomy; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; POD, postoperative day; sMb, serum myoglobin; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; TTE, echocardiography; RV, right ventricle; mPA, main pulmonary artery; LVEF, left ventricular ejection fraction; RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CI, Cardiac output; RPH, residual pulmonary hypertension; PRBCs, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrates; CPB, cardiopulmonary bypass; DHCA, deep hypothermia circulatory arrest; ACC, aortic cross-clamp; UCSD, University of California at San Diego.

media before surgery did not show an association with postoperative AKI (*Table 1*).

The perioperative dynamics of sCr and sMb were thoroughly described (*Figure 2*). There was no statistically significant difference in pre-sMb levels among the different groups. Patients with AKI had higher pre-sMb levels compared to those without AKI. The sMb levels on POD0 increased 14-, 25-, and 29-fold compared to the

Table 2 Relationship between AKI and short-term outcomes

Variables	Full cohort (n=134)	Non-AKI (n=57)	AKI (n=77)	Severe AKI (n=13)	P value^	P value*
Mortality	8 (6.0)	2 (3.5)	6 (7.8)	3 (23.1)	0.505	0.030
ECMO	8 (6.0)	4 (7.0)	4 (5.2)	2 (15.4)	0.943	0.174
Tracheotomy	5 (3.7)	2 (3.5)	3 (3.9)	2 (15.4)	1.000	0.074
MVT (h)	62.6 (39.6–92.5)	44.0 (19.4–92.6)	63.5 (41.9–101.2)	134.5 (45.0–328.8)	0.055	0.007
LOIS (d)	6.0 (4.0–9.0)	5.0 (3.0–8.5)	6.0 (4.0–10.0)	15.0 (5.0–36.5)	0.164	0.025
p-LOHS (d)	19.5 (15.0–26.0)	20.0 (15.5–24.5)	19.0 (15.0–27.0)	19.0 (15.0–40.5)	0.898	0.557

Continuous variables are presented as median (25^{th}–75^{th} percentile) for non-normally distributed data. Categorical variables are reported as frequencies (percentages). AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. ^, (AKI *vs.* non-AKI), patients with AKI (KDIGO stage 1 or higher) compared with patients without AKI. *, (severe AKI *vs.* non-severe AKI), patients with severe AKI (KDIGO stage 2 and 3) compared with patients without AKI and patients with mild AKI (KDIGO stage 1). ECMO, extracorporeal membrane oxygenation; MVT, mechanical ventilation time; LOIS, length of intensive care unit stay; p-LOHS, postoperative length of hospital stay.

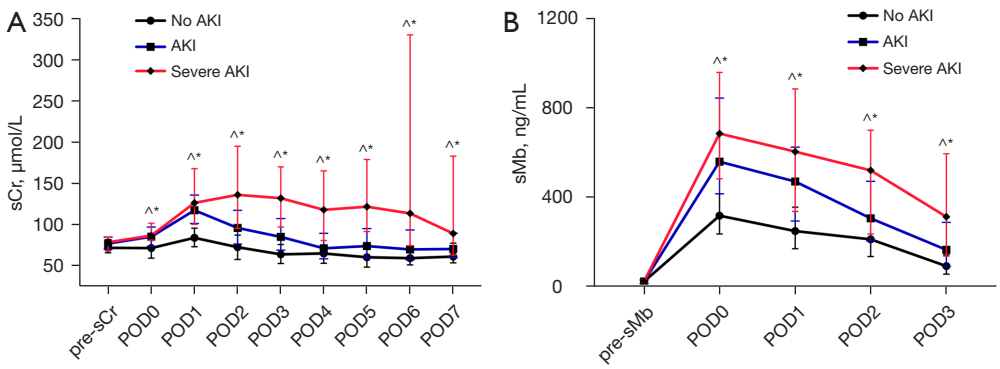

Figure 2 Perioperative quantitative tendency of (A) sCr and (B) sMb. AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. ^, AKI *vs.* non-AKI (P<0.05); *, severe AKI *vs.* non-severe AKI (P<0.05). sCr, serum creatinine; sMb, serum myoglobin; POD, postoperative day; AKI, acute kidney injury.

preoperative levels in the non-AKI, AKI, and severe AKI groups, respectively. The sMb levels in all groups peaked on POD0 and then declined at different rates. On POD3, both the no AKI and AKI groups decreased by about 70%, while the severe AKI group only decreased by 50%. Patients with severe AKI had a higher peak sMb level and a slower elimination rate. The sCr levels peaked at POD1 in the no-AKI and any-AKI groups, while the severe-AKI group showed the highest levels on POD2. Overall, the sCr levels followed the sMb trend with a delay of 0.5–2 days (*Figure 2*, *Table 1*, Table S2). Further analysis revealed moderate positive correlations between Ln(POD1-sCr) and Ln(POD0-sMb) in severe AKI patients (r=0.597; P=0.031) and AKI patients (r=0.422; P<0.001) (*Figure 3*, Tables S3,S4).

The independent risk factors of postoperative AKI and severe AKI

Univariate analysis was performed to identify variables associated with post-PEA AKI (Tables S5,S6). Two multivariate logistic regression models were established (model[a] and model[b]) (*Table 3*). There was no evidence of multicollinearity among the selected variables (Table S7). The Hosmer-Lemeshow test confirmed the appropriateness of the logistic regression models, with P values of 0.431 and 0.797, respectively. Interestingly, the multivariable logistic regression analysis revealed that Ln(POD0-sMb) was an independent risk factor for both AKI (OR =5.174; 95% CI, 2.307–11.603; P<0.001) and severe AKI (OR =4.605; 95%

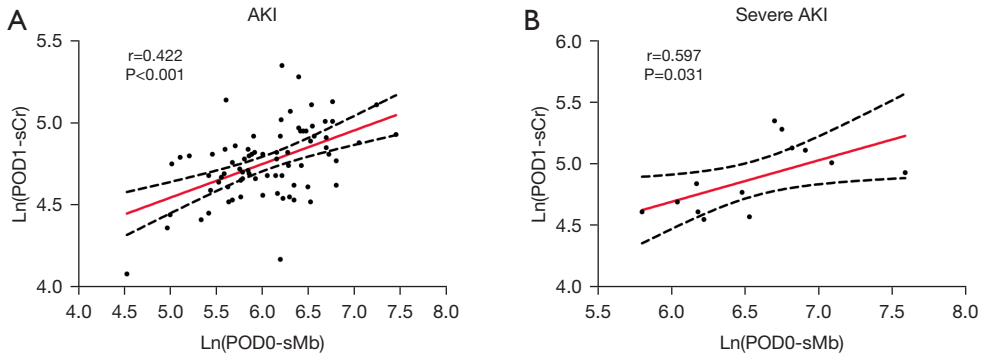

Figure 3 The linear correlation between Ln(POD1-sCr) and Ln(POD0-sMb) in (A) AKI and (B) severe AKI. AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. POD, postoperative day; sCr, serum creatinine; sMb, serum myoglobin; AKI, acute kidney injury.

Table 3 Univariate and multivariate logistic regression models for AKI and severe AKI

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
AKI						
Ln(POD0-sMb)	6.145	2.918–12.943	<0.001	5.174	2.307–11.603	<0.001
Preoperative mPAP (mmHg)	1.055	1.021–1.090	0.001			
Postoperative mPAP (mmHg)	1.054	1.005–1.105	0.031			
Postoperative PVR (dyn·s·cm^{-5}·m^2)	1.003	1.001–1.005	0.007	1.002	1.000–1.004	0.082
Surgery time (min)	1.007	1.002–1.013	0.004	1.005	0.999–1.010	0.103
CPB time (min)	1.010	1.002–1.017	0.008			
ACC time (min)	1.014	1.004–1.024	0.005			
Severe AKI						
Lymphocyte (×10^9/L)	0.327	0.117–0.912	0.033			
Albumin (g/L)	0.854	0.739–0.988	0.033	0.838	0.716–0.980	0.027
Ln(POD0-sMb)	4.460	1.597–12.456	0.004	4.605	1.510–14.048	0.007
ACC time (min)	1.014	1.001–1.027	0.038			

AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. AKI, acute kidney injury; POD0, postoperative day 0; sMb, serum myoglobin; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; OR, odds ratio; CI, confidence interval.

CI, 1.510–14.048; P=0.007). Albumin concentration (OR =0.838; 95% CI, 0.716–0.980; P=0.027) were identified as a protective factor for severe AKI (*Table 3*).

The predictive power of sMb for AKI

To evaluate the predictive power of Ln(POD0-sMb), ROC curves were constructed for AKI and severe AKI, respectively. Regarding the AKI group, the ROC curve showed a slightly lower predictive accuracy for Ln(POD0-sMb) compared to the joint variables [area under the curve (AUC): 0.776 *vs.* 0.789], but the difference was not statistically significant (Delong's test: P=0.489). Similar results were observed for severe AKI whether considering Ln(POD0-sMb) (AUC: 0.737 *vs.* 0.786, Delong's test: P=0.242) or albumin (AUC: 0.734 *vs.* 0.786, Delong's test: P=0.320) (*Figure 4*). The

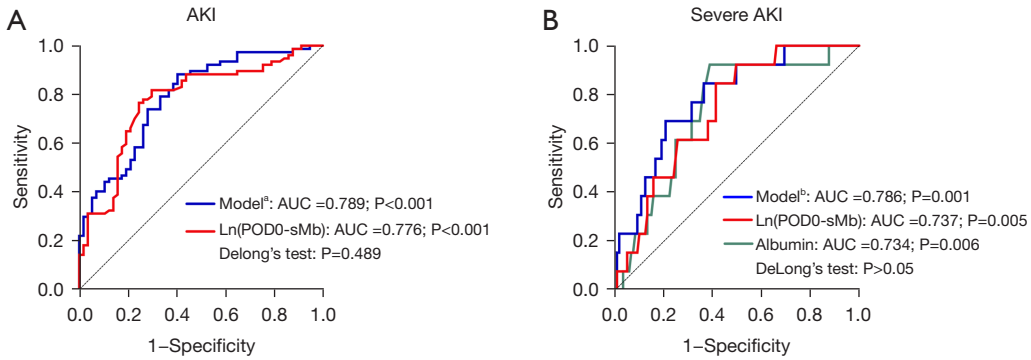

Figure 4 ROC curve for (A) AKI and (B) severe AKI. AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. Model[a]: Ln(POD0-sMb) + postoperative PVR + surgery time (min); AUC =0.789 (0.712–0.866). Model[b]: Albumin (g/L) + Ln(POD0-sMb); AUC =0.786 (0.669–0.902). POD, postoperative day; sMb, serum myoglobin; AKI, acute kidney injury; AUC, area under the curve; ROC, receiver operating characteristic curve; PVR, pulmonary vascular resistance.

Table 4 The cutoff point and corresponding value of Ln(POD0-sMb) in AKI and severe AKI

Group	Cutoff point	Sensitivity	Specificity	Value
Ln(POD0-sMb) in AKI	0.520	0.818	0.702	5.915 (370.554 ng/mL)
Ln(POD0-sMb) in severe AKI	0.435	0.923	0.512	6.039 (419.473 ng/mL)
Albumin in severe AKI	0.535	0.923	0.595	40.350 g/L

Cutoff point was based on the maximum of Youden's index. The numbers in brackets represent the actual corresponding sMb concentrations of logarithmic transformation. AKI is KDIGO stage 1 or higher. Severe AKI is KDIGO stage 2 and 3. POD0, postoperative day 0; sMb, serum myoglobin; AKI, acute kidney injury.

optimal diagnostic cutoff values were determined using the maximum Youden's index. A POD0-sMb concentration >370.544 ng/mL predicted AKI with a sensitivity of 81.8% and a specificity of 70.2%, while a value >419.473 ng/mL predicted severe AKI with a sensitivity of 92.3% and a specificity of 51.2% (*Table 4*). An albumin concentration <40.350 g/L predicted severe AKI with a sensitivity of 92.3% and a specificity of 59.5% (*Table 4*).

Predictors of postoperative sMb level

Covariates of related postoperative sMb with a P value of <0.05 in univariate analysis were included into the multiple linear regression analysis to examine their association with elevated Ln(POD0-sMb) concentration. Among the variables analyzed, CAD, preoperative eGFR, preoperative mPAP and CPB time revealed significant influence on the Ln(POD0-sMb) level (F=11.459, P<0.001, adjusted R^2=0.239) (*Table 5*). No significant impact on postoperative sMb levels was observed for the remaining clinical factors mentioned in this article.

Discussion

In this study, we collected population characteristics of patients undergoing PEA in a single center and investigated the risk factors for AKI after the procedure. Our findings revealed a high incidence of postoperative AKI (57.5%) and mortality (6.0%) following PEA, underscoring the detrimental impact of AKI on short-term outcomes, such as MVT and LOIS. Through multivariate logistic regression analysis, we identified albumin concentration as a protective factor for severe AKI. Interestingly, Ln(POD0-sMb) (log-transformed value of POD0 sMb concentration) was found to be an independent risk factor for both AKI and severe AKI. Furthermore, the value of independent sMb in predicting postoperative AKI is not inferior to the combination of multiple indicators. We determined optimal cutoff values for Ln(POD0-sMb) that could predict the occurrence of AKI (>370.544 ng/mL) and severe AKI (>419.473 ng/mL), as well as albumin concentration (<40.350 g/L). Additionally, we observed that preoperative use of nephrotoxic agents and RPH was not associated with

Table 5 Multiple linear regression of factors related to the Ln(POD0-sMb)

Factors	B	Std.error	β	P value
(Constart)	5.577	0.434		<0.001
CAD	0.420	0.178	0.181	0.020
eGFR (mL/min/1.73 m^2)	–0.009	0.003	–2.242	0.002
Preoperative mPAP (mmHg)	0.009	0.004	0.175	0.032
CPB time (min)	0.003	0.001	0.286	<0.001

F=11.459, P value <0.001, adjusted R^2=0.239. POD, postoperative day; sMb, serum myoglobin; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; mPAP, mean pulmonary arterial pressure; CPB, cardiopulmonary bypass.

postoperative AKI. CAD, preoperative eGFR, preoperative mPAP and CPB time were the predictors of Ln(POD0-sMb) concentration.

CPB is an important auxiliary method for PEA to offer a relatively bloodless field. Blood contact with nonendothelial surfaces of the CPB circuit triggers a robust systemic inflammatory response and shear forces leads to mechanical destruction of red blood cells (21-23). Before removing the obstructive material, the ascending aorta is cross-clamped resulting in a decrease in systemic mean arterial pressure and renal hypoperfusion (24). Together with priming fluid to induce hemodilution, all of these lead to renal ischemia and hypoxia then increase the risk of postoperative AKI. Previous studies have also reported that prolonged CPB duration is a well-established risk factor for the development of postoperative AKI and ACC time is an independent predictor of postoperative mortality after cardiac surgery with CPB (25,26). Notably, the longer CPB duration and ACC time in our center (approximately 1 hour longer than other centers) likely contributed to the higher incidence of AKI compared to similar studies (8,9). However, our study indicated that CPB duration and ACC time was not an independent risk factor for postoperative AKI although there were differences between the two comparisons made, consistent with the findings of Zhang *et al.*'s study (8). Linear regression analysis revealed that the CPB time is a predictive indicator of postoperative myoglobin levels. In our population, CPB time may influence the incidence of AKI by affecting postoperative myoglobin levels.

Currently, no study suggested preoperative or postoperative myoglobin concentrations contributed to the development of postoperative AKI after PEA. But the relationship between myoglobin and other cardiovascular surgical procedures have already been discussed. A higher preoperative myoglobin level increased the risk of the development of AKI after type A aortic dissection repair surgery, valve surgery and coronary artery bypass graft surgery have already been reported (13,14). These patients combined with different organ malperfusion may influence the development of postoperative AKI (27). This phenomenon was not observed in our study. The reasons are that left ventricular ejection fraction between PEA patients with different degrees of AKI was no significant difference, and other diseases leading to organ malperfusion have not been observed.

Our study showed Ln(POD0-sMb) was an independent risk factor for both AKI and severe AKI after PEA. Prolonged surgery results in compression of the back and gluteal muscles, combined with microvascular thrombosis, leading to skeletal muscle ischemia and hypoxia ultimately causing rhabdomyolysis and subsequent release of myoglobin into the bloodstream (28). Undergoing degradation by heme oxygenases, free iron is produced and lead to increased formation of reactive oxygen species (ROS) and peroxidation of tubular cell membrane lipids, causing detrimental changes in renal tubular epithelial function (29-31). Furthermore, concentrated intratubular hemoglobin can form tubular casts that obstruct the renal tubules (32).

Albumin functions as a versatile protein involved in transportation, osmotic regulation, pH buffering, antioxidant activity, immune function, and nutrient transport (33). A meta-analysis showed hypoalbuminemia were associated an elevated risk of morbidity, mortality, AKI, and other clinical outcomes in both hospitalized and surgical patients (34). Studies indicated that preoperative low serum albumin level is an independent risk factor for AKI and preoperative administration of 20% exogenous albumin in patients with preoperative serum albumin levels less than 40.0 g/L increases intraoperative urine output and reduces the risk of developing AKI after off-pump coronary artery bypass grafting (CABG) (35,36). Our findings also indicate that a high serum albumin level is a protective factor against postoperative AKI in patients undergoing PEA surgery, and preoperative albumin concentration should be maintained at or above 40.350 g/L

in CTEPH patients. Research has demonstrated that under physiological conditions, renal tubules can significantly reabsorb albumin which can stimulate DNA synthesis in renal tubular cells, thus maintaining the integrity and function of proximal tubules (37). Albumin at approximately 1% of its serum concentration can increase the survival rate of cultured renal tubular cells (38). During CPB, albumin can maintain plasma oncotic pressure to achieve renal arterial perfusion pressure. It can also regulate inflammatory responses and reduce platelet aggregation, thereby mitigating the risk of renal inflammation and thrombus formation, and protecting the kidneys from injury (38,39). More importantly, human serum albumin (HSA) is the most important antioxidant in human plasma. It can scavenge heme-Fe, reduce the ability of free iron to generate ROS, and protect renal tubular epithelial cells from iron-induced oxidative damage (40,41).

However, clinically notable changes of sCr concentration influenced by various factors often appear days after injury and preclude early therapeutic interventions, necessitating the identification of novel biomarkers for early AKI detection (42). Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), which mediates iron trapping in proximal tubule cells, and urinary hepcidin isoforms, a regulator of iron homeostasis, have shown promise in early AKI detection (43,44). However, these markers are still under research and not widely used in clinical practice. On the other hand, myoglobin, which rises within an hour of skeletal muscle damage and returns to normal within 1 to 6 hours after injury, has been used as an early biomarker for acute myocardial infarction (45). Our study identified that POD0 sMb is an independent risk factor for AKI after PEA and established optimal cutoff values for predicting AKI and severe AKI. Further research, such as the development of nanometer aptamer-based biosensors, may contribute to the pre-diagnosis of AKI (45).

This study has several limitations. It is a retrospective, single-center study, which introduces the potential for bias. The relatively small number of study patients may not fully represent the overall population. Additionally, intraoperative and postoperative biochemical parameters, such as lactic acid and nadir hemoglobin, were not collected or discussed. Furthermore, the causal relationship between sMb and postoperative AKI should be interpreted cautiously, as the study only demonstrated an association. Finally, the clinical factors we included in multiple linear regression analysis can only explain a small portion of the increase of postoperative myoglobin levels after PEA surgery. In the future, we will actively explore additional factors that may influence it.

Conclusions

In conclusion, this study investigated the main risk factors and clinical indicators associated with AKI after PEA and established a risk prediction model for early monitoring of high-risk individuals. The findings suggest that increasing preoperative serum albumin level may be an effective preventive measure for AKI, and elevated POD0 sMb concentration increases the risk of AKI after PEA. Focusing on myoglobin levels may help clinicians identify patients at risk of AKI and enable timely intervention to improve patient prognosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-088) and the requirement for individual consent for this retrospective analysis was waived.

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