

# Prognostic impact of preoperative serum alkaline phosphatase level on a composite of morbidity and mortality after thoracic endovascular aortic repair

## A retrospective study

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### Abstract

**Background:** Serum alkaline phosphatase (ALP) is related to vascular calcification and is known to have a prognostic impact in various cohorts. However, evidence in patients undergoing thoracic endovascular aortic repair (TEVAR) is lacking. Thus, we hypothesized that preoperative serum ALP level could be used for predicting adverse events after TEVAR.

**Methods:** We retrospectively reviewed 167 patients who underwent TEVAR between February 2013 and December 2016. Patients were classified into tertiles according to preoperative ALP level (<69, 69–92, and >92 IU/L). The composite of morbidity and mortality (composite MM) was defined as the presence of one or more of the following: myocardial infarction, cerebrovascular accident, dialysis requirement, pulmonary complication, infection, and mortality within 1 year after TEVAR. The incidence of composite MM was compared among the 3 tertiles, and stepwise logistic regression analysis was performed to evaluate the predictors for composite MM.

**Results:** The incidence of composite MM was 14.5% in the first tertile group, 17.9% in the second tertile group, and 35.7% in the third tertile group ( $P = .016$ ). The third tertile of ALP level (odds ratio [OR] 1.766, 95% confidence interval [CI] 1.074–2.904,  $P = .025$ ) and emergency TEVAR (OR 2.369, 95% CI 1.050–5.346,  $P = .038$ ) remained as independent predictors of composite MM.

**Conclusions:** Our data showed an independent relationship between high preoperative ALP levels and adverse outcomes in patients undergoing TEVAR. This finding might suggest a potential role of ALP level as a risk stratification marker.

**Abbreviations:** AKI = acute kidney injury, ALP = alkaline phosphatase, ALT = alanine aminotransaminase, aneurysm = aortic aneurysm, AST = aspartate aminotransaminase, BB =  $\beta$ -blocker, BMI = body mass index, CAOD = coronary artery occlusive disease, CCB = calcium channel blocker, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, composite MM = composite of morbidity and mortality, Cr = serum creatinine, CRP = C-reactive protein, CSF drainage = cerebrospinal fluid drainage, CVA = cerebrovascular accident, diabetes = diabetes mellitus, dissection = aortic dissection, EF = ejection fraction, HTN = hypertension, ICU = intensive care unit, IMH = intramural hematoma, MI = myocardial infarction, OR = odds ratio, PAU = penetrating aortic ulcer, PCI = percutaneous coronary intervention, POD = duration of postoperative days in hospital stay, RASi = renin-angiotensin system blocker, TEVAR = thoracic endovascular aortic repair, TNALP = tissue-nonspecific isozyme of ALP.

**Keywords:** alkaline phosphatase, aorta, aortic disease, endovascular procedure, thoracic

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## 1. Introduction

The development of complications is considered to be much less frequent after thoracic endovascular aortic repair (TEVAR) than after open surgery. However, potential pitfalls may exist in TEVAR given that it is a vascular procedure and the patient cohort is rarely free from comorbidities. There are a few reports on risk stratifications for perioperative cerebral infarction or 30-day cardiac and cerebrovascular adverse events after TEVAR.<sup>[1,2]</sup> Previously identified risk factors such as a history of ischemic heart disease and stroke, severe atherosclerosis, emergency operation, and elevated serum creatinine level are nonspecific and prevalent. Furthermore, evidence on the prognosis for a more prolonged period than the perioperative course after TEVAR is lacking.

Among the 4 isoforms of alkaline phosphatase (ALP), tissue-nonspecific isozyme of ALP (TNALP) has a pivotal role in bone mineralization.<sup>[3]</sup> It promotes vascular calcification by reducing pyrophosphate, which is a potent inhibitor of medial vascular mineralization.<sup>[4]</sup> In addition, its modulatory effect on the immune system has been implicated in the association between ALP activity and inflammation.<sup>[3,5–7]</sup> Accordingly, the activity of TNALP has been reported to regulate the atherosclerotic process.<sup>[8]</sup> Serum ALP level mainly reflects TNALP<sup>[5]</sup> and shows a strong predictability for poor mid-term and long-term prognosis in patients with kidney disease,<sup>[9,10]</sup> old age,<sup>[11]</sup> myocardial infarction (MI),<sup>[12]</sup> and stroke,<sup>[13,14]</sup> as well as in the general population.<sup>[15]</sup> In patients undergoing percutaneous coronary intervention (PCI), elevated serum ALP level is closely associated with a higher risk of adverse cardiac and cerebrovascular events,<sup>[16]</sup> or mortality and stent thrombosis.<sup>[17]</sup> Considering that aortic disease requiring intervention may be closely related to the calcification and inflammation of the vasculature,<sup>[18,19]</sup> ALP might have a potential role as a prognostic marker in patients undergoing TEVAR, which has never been investigated before.

Hence, we aimed to investigate whether preoperative serum ALP level could be used for predicting adverse events after TEVAR.

## 2. Methods

### 2.1. Study population

After receiving approval and waiver of the informed consent requirement from our institutional review board, we retrospectively reviewed the electronic medical records of all patients who underwent TEVAR of the aortic arch and descending aortic lesions at our university hospital between January 2013 and December 2016 (n=197). Patients with traumatic aortic injury (n=28), preoperative cardiopulmonary resuscitation (n=1), or previous aortic repair within 1 year (n=1) were excluded. Finally, 167 patients were analyzed. To assess risk of postoperative morbidity according to the preoperative serum ALP, we divided patients into 3 groups based on its level (first tertile: ALP <69 IU/L [n=55], second tertile: ALP 69–92 IU/L, [n=56], third tertile: ALP >92 IU/L [n=56]).

### 2.2. TEVAR procedure

TEVAR was performed in a hybrid operating room equipped with angiographic systems. Stent graft including Valiant (Medtronic Vascular, Santa Rosa, CA), Vascutek (Terumo;

Renfrewshire, Scotland, UK), TAG (W.L. Gore and Associates, Flagstaff, AZ), and Zenith TX1/TX2 (Cook Medical, Bloomington, IN) were used. In patients with zone 0, zone 1, or zone 2 landing TEVAR, multiple chimneys or fenestrated endografts were used for debranching. Moreover, in patients undergoing debranching, cerebral regional oxygen saturation was monitored and maintained within 20% of baseline during clamping of vessel by increasing blood pressure and end-tidal carbon dioxide. In patients with landing zone of 3 or 4 that endograft covers T9 to T12, cerebrospinal drainage was performed and spinal cord perfusion pressure was maintained at >60 mm Hg. Systolic arterial pressure was maintained at <100 mm Hg before stent deployment. Furthermore, after deploying the stent, systolic arterial pressure was maintained at >140 mm Hg using volume replacement and nicardipine or norepinephrine, as appropriate. All patients were extubated in the operating room except those with oxygen desaturation or significant hemodynamic instability and transported to the intensive care unit.

### 2.3. Study endpoints

The primary outcome was the incidence of newly developed MI, stroke, dialysis requirement, infection, pulmonary complication, mortality, and a composite (1 or more) of these endpoints within 1 year after TEVAR. MI was defined as an increase in serum peak troponin-T isozyme >5 times the upper limit of normal or a newly developed Q wave. Stroke was defined as the presence of newly developed neurological deterioration induced by embolic, thrombotic, or hemorrhagic brain injury diagnosed by a neurologist. Infection was defined as the occurrence of 1 of the following conditions: pneumonia, sepsis, peritonitis, urinary tract infection, or graft infection. Pulmonary complication was defined as respiratory failure, exacerbation of chronic obstructive disease, or culture-negative pneumonia that required prolonged mechanical ventilation (>24 hours).

### 2.4. Other assessments

Baseline patient characteristics including sex; age; body mass index; comorbidities (hypertension, diabetes mellitus, coronary artery occlusive disease [CAOD], chronic obstructive pulmonary disease, cerebrovascular accident, and chronic kidney disease); preoperative cardiovascular medication; disease acuity; smoking; presence of malperfusion, defined as signs or symptoms of end-organ ischemia; preoperative ejection fraction; and preoperative laboratory data including C-reactive protein (CRP), creatinine, aspartate aminotransferase, and alanine aminotransferase levels were recorded. Perioperative data including the proximal landing zone classified according to Ishimaru classification, spinal drainage, and total procedure time were recorded.

### 2.5. Statistical analysis

All statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY). After the Shapiro–Wilk test for normality, one-way analysis of variance or Kruskal–Wallis test was used to compare continuous variables, as appropriate. Categorical variables were compared using the chi-squared or Fisher exact test. Results are presented as mean ± standard deviation or number of patients (%). Logistic regression analysis to evaluate the predictors for 1-year composite of morbidity and mortality (composite MM) endpoints was conducted on

variables with  $P < .2$  between patients who developed the composite endpoint of morbidity and mortality. For the multivariate analysis, a stepwise selection method was used and variables with  $P < .2$  in the univariate analysis were selected. Predictability was expressed as the odds ratio (OR) and 95% confidence interval (CI). Values of  $P < .05$  were considered statistically significant.

### 3. Results

A total of 197 patients were identified during the study period and 167 patients were finally analyzed. Baseline characteristics were comparable among the groups (Table 1).

Table 2 shows the perioperative data including operative details and immediate postoperative data. The number of patients with proximal landing zone of 0 was significantly different among the 3 groups (0% vs. 1.8% vs. 8.9%,  $P = .048$ ). Combined procedure including head-vessel debranching and cerebrospinal fluid drainage, operation time, immediate postoperative endoleak, acute kidney injury, and postoperative lengths of stay in the intensive care unit and in the hospital were similar among the groups.

Each of the postoperative 1-year morbidity endpoints showed no difference among the groups; however, there was a trend toward a higher incidence of pulmonary complication in the third tertile. The incidence of the composite MM was significantly higher in the third tertile than in the lower 2 tertiles (14.5% vs. 17.9% vs. 35.7%,  $P = .016$ ) (Table 3).

Age, preexisting hypertension, CAOD, chronic kidney disease, the third ALP tertile, combined head-vessel debranching, presence of malperfusion, and emergency operation showed a difference of  $P < .2$  between patients who developed the composite endpoint and those who did not, and were analyzed using logistic regression. In univariate analysis, hypertension, CAOD, the third ALP tertile, malperfusion, and emergency operation were selected for multivariate analysis. The third ALP tertile (OR 1.766, 95% CI 1.074–2.904,  $P = .025$ ) and emergency operation (OR 2.369, 95% CI 1.050–5.346,  $P = .038$ ) remained independent predictors for the composite endpoint of morbidity and mortality (Table 4).

### 4. Discussion

In this retrospective study investigating the association of serum ALP level with 1-year adverse outcomes after TEVAR, the incidence of the composite endpoints of MI, stroke, dialysis requirement, infection, pulmonary complication, and mortality were significantly higher in patients with the third tertile distribution of ALP than in those in the lower 2 tertiles. Moreover, the third tertile of ALP was independently associated with a 1.8-fold increased risk for developing the composite of morbidity endpoints.

Among the 4 isoforms of ALP in humans, TNALP, which is mainly found in the liver and bone, stimulates tissue mineralization.<sup>[3]</sup> Its overexpression in the vasculature is known to induce coronary and aortic calcification, cardiac hypertrophy, and

**Table 1**

**Baseline characteristics.**

	First tertile (n=55)	Second tertile (n=56)	Third tertile (n=56)	P
Female sex	16 (29.1%)	14 (25.0%)	17 (30.4%)	.805
Age (years)	62.02 ± 15.05	63.55 ± 14.60	64.38 ± 12.90	.676
Height (cm)	165.01 ± 9.95	167.17 ± 9.77	165.08 ± 7.66	.377
Weight (kg)	67.11 ± 13.36	69.73 ± 13.00	64.93 ± 11.60	.136
BMI	24.45 ± 3.05	24.83 ± 3.35	23.74 ± 3.36	.200
HTN	42 (76.4%)	41 (73.2%)	41 (74.5%)	.929
DM	7 (12.7%)	5 (8.9%)	5 (9.1%)	.758
CAOD	2 (3.6%)	5 (8.9%)	4 (7.1%)	.629
COPD	0	1 (1.8%)	1 (1.8%)	1.000
CVA	6 (10.9%)	7 (12.5%)	4 (7.1%)	.629
CKD	3 (5.5%)	6 (10.9%)	2 (3.6%)	.284
BB	16 (30.2%)	18 (34.0%)	17 (30.9%)	.906
CCB	18 (34.0%)	22 (41.5%)	19 (34.5%)	.667
RASi	22 (41.5%)	27 (50.9%)	22 (40.0%)	.466
Emergency operation	20 (36.4%)	19 (33.9%)	29 (51.8%)	.114
Smoking	23 (41.8%)	34 (60.7%)	30 (54.5%)	.127
Preoperative EF	63.52 ± 5.67	64.72 ± 5.78	61.28 ± 15.34	.416
Primary aortic disease				
Aneurysm	23 (41.8%)	23 (41.1%)	18 (32.1%)	.505
Dissection	21 (38.2%)	23 (41.1%)	25 (44.6%)	.787
IMH/PAU	11 (20.0%)	10 (17.9%)	13 (23.2%)	.778
Malperfusion	2 (3.6%)	5 (8.9%)	2 (3.6%)	.512
Preoperative CRP	23.91 ± 39.33	40.90 ± 62.10	48.37 ± 75.71	.158
Preoperative Cr	0.89 ± 0.35	1.00 ± 0.45	0.94 ± 0.71	.582
Preoperative AST	28.13 ± 30.05	25.02 ± 11.36	33.07 ± 23.48	.175
Preoperative ALT	21.79 ± 18.34	21.89 ± 14.44	27.82 ± 28.24	.233

Values are presented as mean ± standard deviation or number of patients (%).

ALT = alanine aminotransferase, aneurysm = aortic aneurysm, AST = aspartate aminotransferase, BB = β-blocker, BMI = body mass index, CAOD = coronary artery occlusive disease, CCB = calcium channel blocker, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, Cr = serum creatinine, CRP = C-reactive protein, CVA = cerebrovascular accident, diabetes = diabetes mellitus, dissection = aortic dissection, EF = ejection fraction, HTN = hypertension, IMH = intramural hematoma, PAU = penetrating aortic ulcer, RASi = renin-angiotensin system blocker.

**Table 2**  
**Perioperative data.**

	First tertile (n=55)	Second tertile (n=56)	Third tertile (n=56)	P
Proximal landing zone				
0	0	1 (1.8%)	5 (8.9%)	.048*
1	5 (9.1%)	4 (7.1%)	2 (3.6%)	.467
2	25 (45.5%)	30 (53.6%)	26 (46.4%)	.645
3	22 (40.0%)	14 (25.0%)	14 (25.0%)	.138
4	18 (32.7%)	19 (33.9%)	15 (26.8%)	.683
Debranching surgery	14 (25.5%)	18 (32.1%)	16 (28.6%)	.738
CSF drainage	31 (56.4%)	36 (64.3%)	26 (46.4%)	.163
Operation time	119.40±92.27	119.02±77.13	130.25±107.16	.769
Immediate endoleak	6 (10.9%)	5 (8.9%)	6 (10.7%)	.930
AKI	14 (25.5%)	17 (30.4%)	16 (28.6%)	.845
ICU stay (hour)	74.75±212.81	42.51±95.57	68.67±122.84	.493
POD	14.89±30.19	11.04±9.90	19.11±26.67	.206

Values are presented as the mean ± standard deviation, or number of patients (%).

AKI=acute kidney injury, CSF drainage=cerebrospinal fluid drainage, ICU=intensive care unit, POD=duration of postoperative days in hospital stay.

\*  $P < .05$ .

premature death.<sup>[20,21]</sup> Circulating levels of ALP mainly reflect the activity of TNALP and can be indicative of vascular calcification.<sup>[22]</sup> In this context, higher serum ALP levels have been implicated in the poor prognosis of patients with kidney failure whose mineral metabolism is altered.<sup>[9,10]</sup> The associations of serum ALP levels with mortality were also demonstrated in other patient cohorts, including those with previous MI or stroke, elderly patients, and even in the general population.<sup>[11–15]</sup> Along with such a strong predictability for the natural course and survival of patients with vascular diseases, serum ALP level was recently shown to have a prognostic potential for post-interventional adverse events in patients with CAOD undergoing

percutaneous revascularization.<sup>[16,17]</sup> Consistent with this, we observed a significant relationship between the preoperative serum ALP level and poor clinical outcomes in patients with aortic disease undergoing TEVAR. Considering that the bone-vascular axis might be also perturbed in aortic disease,<sup>[18,19,23]</sup> our finding can be, at least partly, attributable to complications caused by ill-fated vasculature associated with calcification, as in patients with renal and cardiovascular disease.

The literature shows a significant relationship between ALP level and clinical outcomes based on calcification of vascular smooth muscle cells or endothelial cells, which are mainly involved in cardiac and brain vascular health.<sup>[3]</sup> However,

**Table 3**  
**Postoperative 1-year morbidity and mortality.**

	First tertile (n=55)	Second tertile (n=56)	Third tertile (n=56)	P
Myocardial infarction	0	0	3 (5.4%)	.107
Stroke	2 (3.6%)	4 (7.1%)	6 (10.7%)	.398
Dialysis	3 (5.5%)	1 (1.8%)	5 (8.9%)	.249
Infection	2 (3.6%)	2 (3.6%)	3 (5.4%)	1.000
Pulmonary complication	4 (7.3%)	3 (5.4%)	10 (17.9%)	.063
Mortality	5 (9.1%)	3 (5.4%)	5 (8.9%)	.769
Composite	8 (14.5%)	10 (17.9%)	20 (35.7%)	.016*

Values are presented as number of patients (%).

\*  $P < .05$ .

**Table 4**  
**Logistic regression analysis for predictors of composite endpoints of 1-year morbidity and mortality after thoracic endovascular aortic repair.**

	Univariate OR (CI)	P	Multivariate OR (CI)	P
Age	1.021 (0.989–1.055)	.204		
HTN	2.072 (0.708–6.063)	.184	2.274 (0.818–6.323)	.115
CAOD	2.808 (0.640–12.329)	.171	3.111 (0.742–13.050)	.121
CKD	1.147 (0.238–5.528)	.864		
ALP third tertile	1.741 (1.049–2.890)	.032	1.766 (1.074–2.904)	.025
Debranching surgery	1.576 (0.658–3.773)	.307		
Malperfusion	3.211 (0.741–13.921)	.119	3.177 (0.758–13.319)	.114
Emergency	2.217 (0.955–5.148)	.064	2.369 (1.050–5.346)	.038

Values are presented as odds ratio (95% confidential interval).

ALP=alkaline phosphatase, CAOD=coronary artery occlusive disease, CI=confidence interval, CKD=chronic kidney disease, HTN=hypertension, OR=odds ratio.

vascular mineralization may not be solely attributed to these cells. Other vascular cells of mesenchymal origin, including pericytes and fibroblasts, can also undergo osteochondrogenic transformation induced by ALP activity.<sup>[24]</sup> Hence, we evaluated multiple clinical endpoints instead of only cardiac and cerebrovascular morbidity, unlike in previous studies.

The higher burden of systemic inflammatory status that was reported to be associated with elevated ALP activity could trigger the development of end-organ disease.<sup>[3,12,14]</sup> Furthermore, ALP has been reported to be associated with CRP, which reflects inflammation.<sup>[7,25]</sup> In addition to the involvement of vascular cells, increased activity of TNALP in leukocytes has been implicated in higher serum ALP levels in sepsis and other acute inflammatory conditions.<sup>[6]</sup> Particularly, B-cell activity, which is known to be strongly influenced by factors regulating osteoblasts and osteoclasts, may play an important role.<sup>[5]</sup> Accordingly, increased serum ALP level is considered a cellular response to inflammatory stimuli such as bacterial invasion.<sup>[3]</sup> In this regard, there are several reports on the association of higher serum ALP level and infection-related death both in patients undergoing dialysis<sup>[26]</sup> and in those with normal renal function.<sup>[27]</sup> Our finding of a close relationship between ALP level and the composite of endpoints could also be at least partly attributable to infection and sepsis-related mortality, although there was no significant association of ALP level and infection per se. The exact pathophysiologic mechanisms of the interplay between ALP level and susceptibility to infection are not known; however, increased expression of ALP induced by pathogens was reported to trigger the Toll-like receptor 4/nuclear factor- $\kappa$ B pathway, resulting in the production of pro and anti-inflammatory cytokines.<sup>[3,28]</sup> In this regard, whether ALP activates or inhibits the inflammatory reaction should be postulated cautiously through further investigations. The conflicting evidences about ALP level and renal outcomes should be considered in the same context. A renoprotective action of ALP through reduced inflammation and oxidative stress was reported,<sup>[3,6,29]</sup> whereas a strong association was found between higher ALP level and poor prognosis in patients with kidney disease.<sup>[9,10,20,26]</sup> Our analysis revealing a biphasic relationship between the ALP tertiles and dialysis requirement, despite the lack of statistical significance, may be explained in this context.

Among the outcomes of our analysis, pulmonary complication was the most closely linked factor to ALP level, although it did not reach statistical significance ( $P=.063$ ). In accordance with our result, a previous report observed that serum ALP level returned to normal according to the cure of the lung pathology.<sup>[30]</sup> Moreover, several studies reported serum ALP level as a diagnostic marker in various pulmonary diseases such as chronic interstitial lung disease and idiopathic pulmonary fibrosis.<sup>[31–33]</sup> Calcification of endothelial cells, pericytes, and fibroblasts in the alveolar-capillary structure and bronchial tree could have induced respiratory failure, exacerbation of chronic obstructive disease, or pneumonia in our patients. The higher grade of inflammation in patients with elevated ALP levels could also involve the lung parenchyma, alveolar capillary unit, and airways, leading to adverse clinical events.<sup>[7]</sup>

The role of serum ALP level as a prognostic factor for adverse outcomes has been demonstrated in various cohorts. Serum ALP level was reported to be associated with coronary disease and also with increased mortality in elderly men.<sup>[11]</sup> In a recent study conducted in patients after PCI, higher serum ALP levels predicted mortality, MI, and stent thrombosis.<sup>[17]</sup> In addition,

elevated serum ALP level was found to be an independent risk factor of major adverse cardiac or cerebrovascular events after primary PCI in patients with ST-segment elevation MI.<sup>[16]</sup> However, serum ALP level did not have a prognostic value for predicting adverse outcomes such as major adverse cardiac events, mortality, MI, or revascularization after off-pump coronary artery bypass surgery.<sup>[34]</sup> This discrepancy may be due to the different inflammatory process between PCI and open cardiac surgery. As serum ALP level was reported to reflect inflammation, a different inflammatory process may be an important factor for predicting adverse outcomes by using serum ALP level. Considering that serum ALP level reflects inflammation and vascular calcification, this parameter could be expected to have a prognostic value for predicting adverse outcomes after TEVAR. We first demonstrated that the occurrence of 1 or more among MI, stroke, dialysis, infection, and mortality within 1 year after TEVAR can be strongly predicted by high preoperative serum ALP levels, which is the strength of the present study.

This study has several limitations. First, the small sample size may reduce validity and reliability of the current result. Lack of significant differences in the risk of each morbidity endpoints among the groups could also be attributable to small sample size. Second, incomplete adjustment of the confounding factors can also be a threat to reliability of the result. We observed no differences in the preoperative liver enzymes and pre-existing renal insufficiency which are closely related to ALP level among the groups. However, other factors that can affect the result, such as bone disease, malnutrition, or infection, were not included in analysis because of our insufficient dataset, which makes possibility of consequent bias cannot be excluded. Similarly, a greater portion of patients had proximal landing zone 0 in the third tertile group. Although the primary outcome was not different according to the proximal landing zone, the difference among the groups could at least partly confound the result. Further studies on larger sample size and a thorough control of confounders should be conducted to get more conclusive results.

In conclusion, serum ALP level was independently associated with an increased risk of a composite MM during 1 year after TEVAR, along with emergency operation. This result suggests that serum ALP level has a prognostic value for adverse outcomes after TEVAR, and that the possible mechanisms for this prognostic effect might be associated with inflammation and vascular calcification; however, this needs to be clarified in further investigations.

### Author contributions

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