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# Preoperative Predictors of Long-Term Mortality after Elective Endovascular Aneurysm Repair for Abdominal Aortic Aneurysm

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**Objective:** This study aimed to clarify long-term mortality and its predictors in patients with abdominal aortic aneurysm (AAA) who underwent endovascular aneurysm repair (EVAR).

**Materials and Methods:** Patients with AAA who underwent elective EVAR at Tokyo Medical and Dental University hospital between 2008 and 2011 were reviewed. The patients' data were retrospectively collected from medical records.

**Results:** Sixty-four patients were identified for this study. In long-term follow-up, the survival rate was significantly lower in patients with high preoperative C-reactive protein (CRP) levels. Patients with obstructive lung disease (FEV<sub>1</sub>/FVC <70%) or anemia tended to have a poorer prognosis but the association was not statistically significant. Age, concurrent hyperlipidemia, and blood pressure levels were not predictors of mortality rates.

**Discussion:** High CRP level, COPD, and anemia reflect inflammation, which is associated with the pathogenesis of AAA. These inflammatory markers are predictors of long-term mortality after EVAR for AAA as well as for other diseases.

**Conclusions:** A high preoperative CRP level was a predictor of increased long-term mortality in patients with AAA who underwent EVAR. No specific leading causes of death were identified for this increase in the mortality rate.

**Keywords:** endovascular aneurysm repair, abdominal aorta aneurysm, C-reactive protein, mortality

## Introduction

Abdominal aortic aneurysm (AAA), a common disorder in the aged population, is an indication for open or endovascular surgical repair if it is considered to be at risk of rupture.<sup>1–3)</sup> In our hospital, endovascular aortic aneurysm repair (EVAR) was started in 2008. The greatest advantage of EVAR is its minimally invasive nature. Some studies have reported various predictors of long-term mortality after EVAR for AAA,<sup>4–6)</sup> but few studies have assessed Asian ethnic populations. This study aimed to investigate the long-term results of patients with AAA who underwent EVAR and to determine the effect of preoperative factors on the long-term survival of these patients.

## Materials and Methods

### Subject recruitment

The study retrospectively identified patients with AAA treated with elective EVAR at the Tokyo Medical and Dental University Hospital (TMDU) between January 2008 and December 2011.

### Data collection

Patient data, including diagnosis, age, sex, smoking history, operation procedure, and prognosis, were obtained from the medical records. For the patients who had not visited TMDU for follow-up for over 1 year, we sent letters asking about their state of health. The following preoperative clinical laboratory parameters were evaluated: C-reactive protein (CRP), hematology, blood chemistry, hemoglobin A1c (HbA1c), and pulmonary function tests.

### Statistical analysis

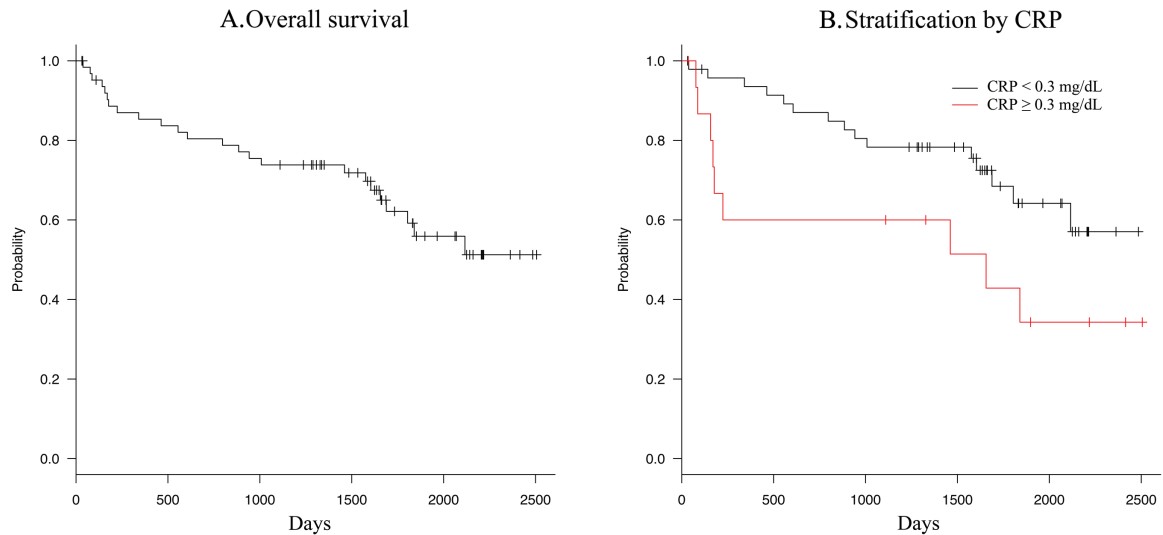
Overall survival was estimated using the Kaplan–Meier method and was compared between the groups with the log-rank test. Statistical analyses were performed using R (The R Foundation for Statistical Computing, version 3.2.2)<sup>7)</sup> with EZR (Saitama Medical Center, Jichi Medical University),<sup>8)</sup> which is a graphical user interface for R.

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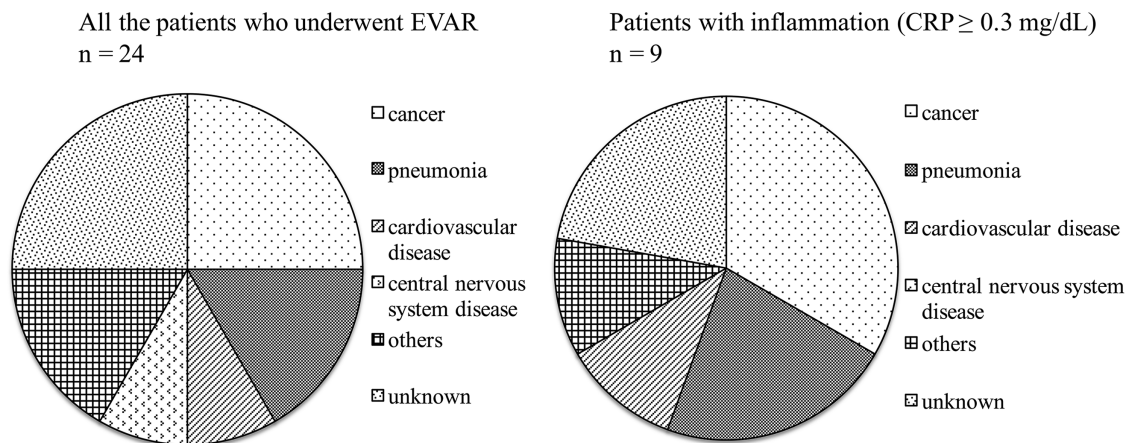
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Received: December 12, 2015; Accepted: February 7, 2016  
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**Fig. 1** Survival in patients with AAA undergoing EVAR. **(A)** Overall survival in patients with EVAR. The overall 5-year survival rate was 0.592 (95% CI: 0.440–0.715). **(B)** Patients with preoperatively elevated CRP (CRP ≥ 0.3 mg/dL) had poorer prognosis. The 5-year survival rate of patients with elevated CRP was 0.429 (95% CI: 0.170–0.667) and that of patients with normal CRP was 0.642 (95% CI: 0.458–0.777). AAA: abdominal aortic aneurysm; EVAR: endovascular aneurysm repair; CRP: C-reactive protein; CI: confident level



**Fig. 2** Causes of death. The causes of death in patients with preoperatively elevated CRP (CRP ≥ 0.3 mg/dL) were similar to those in all the patients with AAA undergoing EVAR. CRP: C-reactive protein; AAA: abdominal aortic aneurysm; EVAR: endovascular aneurysm repair

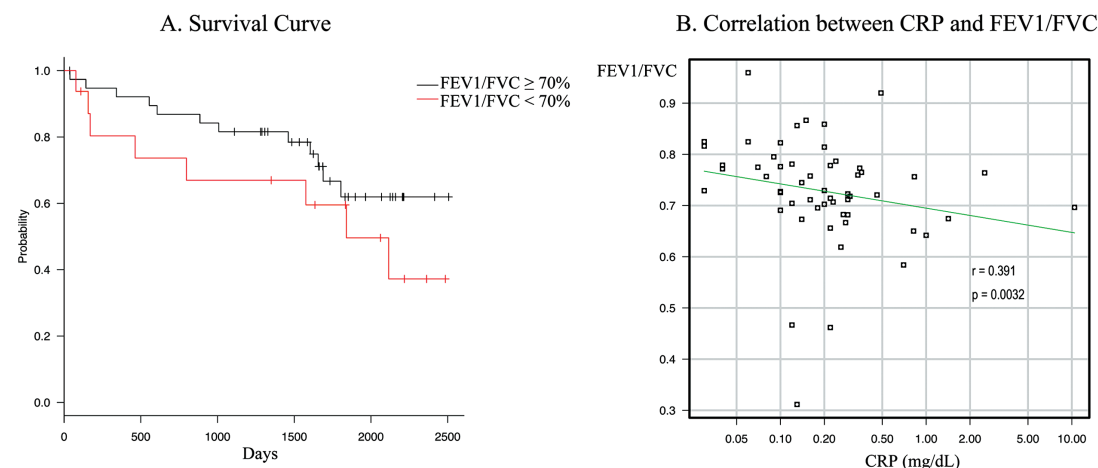
P values of less than 0.05 were regarded as statistically significant.

The protocol for the study was reviewed and approved by the Ethics Committees of the Tokyo Medical and Dental University (approved number 2050).

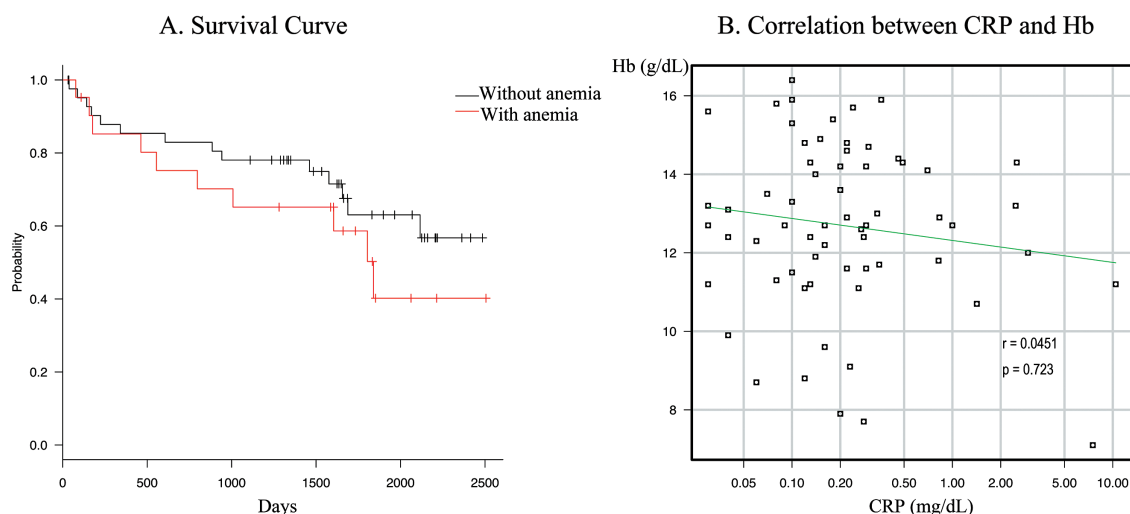
## Results

Sixty-four (males, 52 (81%); mean age,  $75.6 \pm 7.5$  years; females, 12 (19%); mean age,  $78.0 \pm 9.2$  years) patients were included in this study. Only one patient had been given a diagnosis of inflammatory AAA, however we believe that

this subject can be classified as not having inflammatory AAA when EVAR was performed. Because the EVAR was performed for aneurysm after prosthetic graft replacement treated with open surgery for inflammatory AAA 7 years previously, and arteries has been well for 6 years after EVAR. Two patients had postoperative complications and one patient died of renal failure. Neither aneurysm related death nor endoleak occurred after EVAR. Eight patients underwent reoperation. The average follow-up period for living subjects was  $1801.3 \pm 390.0$  days. The overall 5-year survival rate was 0.592 (95% confidence level (CI): 0.440–0.715) (Fig. 1A).



**Fig. 3** Patients with obstructive lung diseases ( $FEV_1/FVC < 70\%$ ). **(A)** Patients with obstructive lung diseases ( $FEV_1/FVC < 70\%$ ) tended to have poorer prognosis but this association was not statistically significant ( $p = 0.209$ ). The five-year survival rate of patients with obstructive lung diseases was 0.595 (95% CI: 0.309–0.795) and that of patients without obstructive lung diseases was 0.619 (95% CI: 0.415–0.770). **(B)** Correlation between CRP levels and  $FEV_1/FVC$ . Patients with obstructive pulmonary function tended to have high preoperative CRP levels. Spearman's rank correlation coefficient =  $-0.391$  and  $p = 0.0032$ . CI: confident level; CRP: C-reactive protein



**Fig. 4** Patients with anemia (male: serum hemoglobin  $< 13.8$  g/dL, female: serum hemoglobin  $< 12.0$  g/dL). **(A)** Patients with anemia tended to have poorer prognosis but this association did not reach statistical significance ( $p = 0.282$ ). The 5-year survival rate of patients with anemia was 0.503 (95% CI: 0.248–0.712) and that of patients without anemia was 0.630 (95% CI: 0.438–0.773). **(B)** Correlation between CRP and hemoglobin levels. There were no correlations between CRP and hemoglobin levels. Spearman's rank correlation coefficient =  $-0.0451$  and  $p = 0.723$ . CI: confident level; CRP: C-reactive protein

In long-term follow-up, the survival rate was significantly ( $p = 0.0435$ ) lower in patients with high preoperative CRP levels ( $CRP \geq 0.3$  mg/dL,  $n = 16$ ) (Fig. 1B). In these patients with elevated CRP levels, the causes of death were similar to those in the general population undergoing EVAR (Fig. 2).

There were 16 patients with obstructive lung disease ( $FEV_1/FVC < 70\%$ ). According to the classification of airflow limitation severity,<sup>9</sup> nine patients (56%) were Mild

(GOLD 1), six patients (38%) were Moderate (GOLD 2), and one patient (6%) were Very Severe (GOLD 4). Pulmonary function tests had been not performed in nine patients. Patients with obstructive lung disease tended to have poorer prognosis than patients without obstructive lung disease ( $FEV_1/FVC \geq 70\%$ ,  $n = 39$ ) but this association was not statistically significant ( $p = 0.209$ ) (Fig. 3A). Some correlation was observed between the severity of airflow limitation and CRP levels ( $r = -0.391$ ,  $p = 0.0032$ ) (Fig. 3B).

Patients with anemia (male: serum hemoglobin <13.8 g/dL, female: serum hemoglobin <12.0 g/dL,  $n = 21$ ) tended to have poorer prognosis but this association was also not statistically significant ( $p = 0.282$ ) (Fig. 4A). No correlation was noted between the serum hemoglobin level and CRP levels ( $r = -0.0451$ ,  $p = 0.723$ ) (Fig. 4B).

Patient age, hyperlipidemia, and blood pressure at admission did not affect mortality (data not shown) in this study.

## Discussion

The mechanisms for AAA formation are still incompletely understood. Transmural inflammation observed in AAA involves a variety of inflammatory cell types, with macrophages and lymphocytes being the most prominent and mast cells and neutrophils showing lower migration.<sup>10,11</sup> The majority of the infiltrating lymphocytes comprises clusters of differentiation 4 positive (CD4+) T cells, with T helper 1 (Th1) and Th17 cells being predominant, whereas infiltration by anti-inflammatory T regulatory ( $T_{reg}$ ) and Th2 cells occurs to a lesser extent.<sup>10,11</sup> In the aneurysmal aortic wall, a macrophage phenotype imbalance exists with a greater number of proinflammatory M1 macrophages than anti-inflammatory M2 macrophages.<sup>10,11</sup> Further, the levels of M1-associated proinflammatory cytokines, such as interleukin (IL)-1 $\beta$ , IL-6, IL-8, interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , and monocyte chemoattractant protein-1 (MCP-1), have been shown to be increased in human aneurysmal tissue and serum.<sup>10,11</sup>

In our study, high preoperative CRP levels were observed in 23% of the patients with AAA who underwent EVAR. Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine IL-6.<sup>12</sup> Therefore, an elevation in CRP levels and the presence of AAA share the same pathological pathways. We demonstrated that among patients with AAA who underwent EVAR, a high preoperative CRP level was a predictor of increased mortality. Numerous studies have demonstrated a predictive relationship between increased CRP production and future atherothrombotic events, including coronary events, stroke, and progression of peripheral arterial disease.<sup>12</sup> In our study, not only cardiovascular diseases and central nervous system disease but also cancer and pneumonia were causes of death contributing to the rise in the mortality rate.

In our study, approximately 36% patients showed obstructive lung function ( $FEV_1/FVC < 70\%$ ), and most of these patients were thought to have undiagnosed chronic obstructive pulmonary disease (COPD) because they failed to report obstructive respiratory diseases such as COPD or bronchial asthma at the time of medical history taking. COPD is mainly caused by smoking, and a low-grade

systemic inflammatory response is evident in smokers as confirmed by numerous population-based studies.<sup>13,14</sup> Elevated serum levels of CRP, fibrinogen, and IL-6 as well as increased counts of WBC have been reported in patients with COPD.<sup>13,14</sup> Thus, COPD and AAA share the same pathological pathways. In fact, there is a strong association between smoking and AAA, with active smokers being more susceptible to developing AAA as compared with non-smokers and previous smokers. This is reflected by a more than four-fold increase in the prevalence of AAA in lifelong smokers than in non-smokers.<sup>15</sup>

Approximately 30% patients showed anemia in our study (male: serum hemoglobin <13.8 g/dL, female: serum hemoglobin <12.0 g/dL), and most of them were thought to have anemia of chronic disease, because the anemia was generally classified as normocytic normochromic. [88% of the patients with anemia] It is known that local iron retention and altered iron recycling associated with high hepcidin and low transferrin systemic concentrations could lead to reduced levels of circulating hemoglobin in AAA patients.<sup>16</sup> The increase in hepcidin secretion in response to infectious or inflammatory stimuli is responsible for the characteristic hypoferrremia observed in inflammation. IL-6 is the main cytokine that stimulates hepcidin synthesis during infection and inflammation.<sup>17,18</sup> Therefore, anemia and AAA also share the same pathological pathways.

In the present study, patients with obstructive lung disease or anemia tended to have poorer prognosis but this association did not reach statistical significance. The reason for nonsignificant difference is in part attributed to small sample size. In addition most of the patients with COPD were Mild (GOLD 1) or Moderate (GOLD 2) according to the classification of airflow limitation severity.<sup>9</sup> In fact, they are thought to have little symptoms and therefore to have been undiagnosed until EVAR was performed. AAA, high CRP levels, COPD, and anemia share common inflammatory pathways as mentioned above, but the pathogenetic mechanisms of these disorders are not identical. Interestingly, we did not observe strong correlations between CRP levels,  $FEV_1/FVC$ , or hemoglobin levels in the patients with AAA. Our data showed that increased levels of inflammatory markers suggested poorer prognosis in patients with AAA undergoing EVAR, but the underlying mechanisms were not clear as multifactorial pathogenetic pathways may be involved in these disease interactions. In terms of systemic inflammation, the effect of statins in reducing the risk of cardiovascular disease is well established due to their anti-inflammatory properties. Previous studies reported that statins are associated with greater long-term survival after open AAA surgery and after EVAR.<sup>19,20</sup> Because evidences for dedicated use of statins in patients with AAA are not enough, our results

would justify further investigation for the effects of statins on the outcomes of surgical intervention for AAA especially in the patients with high CRP levels.

In a previous report, 5-year survival rate after open AAA repair was 67%.<sup>21)</sup> Cardiac disease and cancer, followed by stroke, pulmonary disease, and renal failure were the principal causes of death in AAA patients.<sup>21)</sup> It is also reported that systemic inflammation might influence results after open surgery for aortic aneurysms.<sup>22,23)</sup> Our results for EVAR showed similar results with these previous report from western countries and our result of long term follow up for patients with AAA undergoing open surgery (manuscript in preparation).

Prognosis of inflammatory AAA is significantly worse compared to atherosclerotic AAA in general<sup>24)</sup> and indication of EVAR for inflammatory AAA is still controversial. We could not analyze the long term results of EVAR for inflammatory AAA, because there were few subjects.

## Conclusions

A high preoperative CRP level was a predictor of increased mortality in patients with AAA who underwent EVAR. No specific leading causes of death for this increase in the mortality rate were identified.

## Ethics Approval

This study was approved by the ethical committee of the Tokyo Medical and Dental University (approval number 1957).

## Disclosure Statement

All authors have no conflicts of interest to declare.

## Author Contributions

Study conception: YS

Data collection: NS, TK, YI, YS

Analysis: NS, YS

Investigation: NS, TK, YI, YS

Writing: NS, YS

Critical review and revision: All authors

Final approval of the article: All authors

Accountability for all aspects of the work: All authors

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