Peak C-Reactive Protein Level Predicts Long-Term Outcomes in Type B Acute Aortic Dissection


Abstract—Acute aortic dissection (AAD) is associated with an inflammatory reaction, as evidenced by elevated inflammatory markers, including C-reactive protein (CRP). The association between the peak CRP level and long-term outcomes in type B AAD has not been systematically investigated. The purpose of this study was to investigate whether the peak CRP level during admission predicts long-term outcomes in type B AAD. We conducted a clinical follow-up study of type B AAD. We divided the study population into 4 groups according to the tertiles of peak CRP levels (T1: 0.60 to 9.37 mg/dL; T2: 9.61 to 14.87 mg/dL; T3: 14.90 to 32.60 mg/dL; and unavailable peak CRP group). Multivariate Cox regression analysis was applied to investigate whether the tertiles of peak CRP predict adverse events even after adjusting for other variables. A total of 232 type B AAD patients were included in this analysis. The median follow-up period was 50 months. CRP reached its peak on day 4.5±1.7. Mean peak CRP values in T1, T2, and T3 were 6.4±2.4, 12.0±1.5, and 19.5±4.0 mg/dL, respectively. There were 65 events (39 deaths and 26 aortic events) during the follow-up. T3 and T2 (versus T1) were strong predictors of adverse events (T3: hazard ratio: 6.02 [95% CI: 2.44 to 14.87], P=0.0001; T2: hazard ratio: 3.25 [95% CI: 1.37 to 7.71], P=0.01) after controlling for all of the confounding factors. In conclusion, peak CRP is a strong predictor for adverse long-term events in patients with type B AAD.

Key Words: C-reactive protein ■ peak CRP ■ initial CRP ■ type B acute aortic dissection ■ long-term outcomes

Type B acute aortic dissection (AAD) is often successfully managed by medical therapy during the acute phase, with a lower in-hospital mortality rate compared with type A AAD.1 However, the long-term prognosis of type B AAD is associated with both higher morbidity and mortality.2–5 In an attempt to identify high-risk patients, several predictors of long-term adverse events in type B AAD have been reported.6–9 These predictors include false lumen closure status and imaging studies, such as computed tomography (CT). However, the anatomy of the dissection is often complex, making it difficult to estimate the severity of disease by 2D imaging markers alone.

AAD is associated with an inflammatory reaction,10–12 as evidenced by a significant elevation in inflammatory markers, including C-reactive protein (CRP).13–16 Although CRP levels during hospital admission show significant temporal variations, the peak CRP level has been reported to be a useful marker to estimate the whole severity of acute illness or to predict adverse events.17,18 However, the association between peak CRP and long-term outcomes in type B AAD has not been systematically investigated. Therefore, the purpose of this study was to investigate whether the peak CRP level predicts long-term outcomes in type B AAD.

Methods

Patients and Follow-Up

We identified type B AAD patients from hospital admission records between December 1989 and December 2008. The inclusion criteria were type B AAD presenting within 14 days of symptom onset and CT with contrast confirming a dissected descending aorta containing both a true and false lumen. The exclusion criteria were an in-hospital death in the index admission and loss to follow-up. Follow-up was performed via office visit, letter, or telephone contact. The day of the index discharge was determined as the beginning of follow-up. The study primary end points were all-cause death and aortic events, such as surgery of the thoracic aorta (ascending, arch, or descending), recurrence of an aortic dissection, and an aortic rupture. Because other follow-up studies in type B AAD had used all-cause mortality as the end point, we adopted all-cause mortality as the end point.19,19,20 However, we also collected information about the cause of each death, which allowed us to perform a secondary analysis using cardiovascular death and aortic events as the secondary end points. Patients were followed until meeting a study primary end point (death or an aortic event) or until the study end date (April 2009). Patients who did not experi-
ence an outcome of interest were censored at the last known date of contact.

This study was performed in accordance with the Helsinki Declaration and was approved by the internal review board. All of the study patients had previously granted permission for use of their medical charts for research purposes.

Definition of Peak CRP
Circulating CRP was mostly measured daily or every other day until it reached its initial peak in our institution. Initial peak CRP level was defined as the peak CRP. From December 1989 to November 2003, CRP was measured by turbidimetric immunoassay (Iatron CRP-TIA, Iatron) using an autoanalyzer (JCA-RX20, JEOL Ltd). From November 2003 to December 2008, CRP was measured by latex agglutination nephelometry (NanopiaCRP, Sekisui Medical) using an autoanalyzer (JCA-BM2250, JEOL Ltd). When the admission or predischarge CRP level was higher than the rest of the CRP levels, we were unable to determine the peak CRP level. We divided the patients who had peak CRP levels into 3 groups according to the tertiles of peak CRP, with T1 being the lowest and T3 being the highest (CRP level; T1: 0.60 to 9.37 mg/dL; T2: 9.61 to 14.87 mg/dL; T3: 14.90 to 32.60 mg/dL). The patients who did not have peak CRP levels were included in an unavailable peak CRP group (UG). The initial CRP level, which was measured after admission, was defined as the initial CRP.

Definition of Other Clinical Criteria
Clinical criteria were defined as described here. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or medical treatment for hypertension before admission. Hyperlipidemia was total cholesterol level >220 mg/dL, low-density lipoprotein cholesterol level >140 mg/dL, or treatment for hyperlipidemia before admission. Diabetes mellitus was hemoglobin A1c level >6.5% or treatment for diabetes mellitus before admission. Estimated glomerular filtration rate was calculated from the serum creatinine level, age, weight, and sex, according to the Cockcroft-Gault formula, and estimated glomerular filtration rate \( \leq 60 \text{ mL/min} \) was considered impaired renal function. CT scan with intravenous contrast was performed \( \geq 1 \) time in all of the patients. The initial examination was used for the statistical analysis. Partial enhancement of the false lumen was defined as a nonthrombosed type, and an intramural hematoma of the aorta was included as a thrombosed type. Maximum aortic diameter of the dissected aorta was also measured in all of the patients.

Statistical Analysis
Data are presented as frequencies and percentages for categorical variables and mean±SD for continuous variables. Patient characteristics are compared between the groups divided by the tertiles of peak CRP. Parametrical data were compared using a 1-way ANOVA, whereas nonparametrical data were compared using the Kruskal-Wallis test. Categorical data were compared using the \( \chi^2 \) test. The Kaplan–Meier curves stratified according to the tertiles of peak CRP were constructed. Multivariate Cox regression analysis was applied to investigate whether the tertiles of peak CRP predict adverse events even after adjusting for other variables using 3 models. In model 1, we selected independent variables by a statistical selection. We used significantly different characteristics among the 4 groups as the independent variables. In model 2, we selected independent variables by a clinical selection. We adopted known factors such as age, sex, maximum aortic diameter, false lumen closure status, the extent of dissection, statin use, antihypertensive medications at discharge, and impaired renal function as independent variables.\(^{1,4,6–9,22}\) The difference between CRP measurements was also adopted in this model. In model 3, we selected independent variables by a combination of statistical selection and clinical selection. We adopted all of the independent variables used in model 1 and model 2. All of the variables were simultaneously adjusted in 1 step. Hazard ratios (HRs) and the 95% CI were calculated. We constructed a conventional receiver operating characteristic curve to analyze peak CRP levels to determine the cutoff points that yielded the highest combined sensitivity and specificity with respect to distinguishing patients with adverse events from those without such events. A \( P<0.05 \) was considered statistically significant. All of the analyses were performed using statistical software, SPSS 13.0/Windows (SPSS Inc).

Results
Between December 1989 and December 2008, there were 263 patients with type B AAD admitted to Saitama Medical Center. Ten patients were excluded from the study because of the lack of critical information, such as a CT. Nine patients died during the index admission. Twelve patients were lost to follow-up. Thus, a total of 232 type B AAD patients were included in this analysis. The median follow-up for the 232 patients was 50 months. Although peak CRP levels were available in 200 patients, peak CRP levels were unavailable in 32 patients (admission CRP levels higher than the rest of the CRP levels \( [n=22]; \) predischarge CRP levels higher than the rest of the CRP levels \( [n=8]; \) serial measurements of CRP data not obtained \( [n=2] \)). The 200 patients who had peak CRP levels were divided into 3 groups according to the tertiles of peak CRP, with T1 being the lowest and T3 being the highest. The 32 patients who did not have peak CRP levels were included in a UG. A patient flowchart is shown in Figure S1 (available in the online Data Supplement at http://hyper.ahajournals.org).

In 88% of the patients who had an available peak CRP (176 of 200), CRP reached its peak between day 3 and day 6 (day: 4.5±1.7). The correlation coefficient between initial CRP levels and peak CRP levels was 0.23 (Spearman rank coefficient; \( P=0.001 \)). The clinical characteristics among all, T1, T2, T3, and UG are shown in Table 1. Mean peak CRP values in the total population, T1, T2, and T3 groups were 12.6±6.1, 6.4±2.4, 12.0±1.5, and 19.5±4.0 mg/dL, respectively. Initial CRP levels, time from onset to admission, being overweight (body mass index \( >25 \text{ kg/m}^2 \)), current smoking, impaired renal function at admission, white blood cell counts, heart rate at discharge, and diuretics as an antihypertensive medication at discharge were significantly different among groups. The Kaplan–Meier curves stratified according to the tertiles of peak CRP and unavailable peak CRP are shown in the Figure. Log-rank testing revealed a significant increase in adverse events in the T3 group and UG as compared with the T1 group \( (P=0.0001 \text{ for T3 versus T1}; P=0.0004 \text{ for UG versus T1}) \). There were 65 events (39 deaths and 26 aortic events) during the follow-up period (Table S1).

Multivariate Cox regression analysis was performed in 3 ways. In model 1, the tertiles of peak CRP and significant confounding factors, such as tertiles of initial CRP, time from onset to admission, being overweight, current smoking, impaired renal function at admission, white blood cell counts, heart rate at discharge, and diuretics as antihypertensive medication at discharge, were adopted as independent variables (Table 2). UG, T3, and T2 (versus T1) were strong predictors of adverse events (UG: HR: 7.07 [95% CI: 2.60 to...
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All</th>
<th>Lowest Tertile (T1)</th>
<th>Middle Tertile (T2)</th>
<th>Highest Tertile (T3)</th>
<th>Unavailable Peak (UG)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CRP range, mg/dL</td>
<td>0.60 to 32.60</td>
<td>0.60 to 9.37</td>
<td>9.61 to 14.87</td>
<td>14.90 to 32.60</td>
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<td></td>
</tr>
<tr>
<td>No.</td>
<td>232</td>
<td>67</td>
<td>67</td>
<td>66</td>
<td>32</td>
<td>0.32</td>
</tr>
<tr>
<td>Median follow-up period, mo</td>
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<td>71</td>
<td>50</td>
<td>38</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Peak CRP, n, mg/dL</td>
<td>12.6±6.1, 200</td>
<td>6.4±2.4, 67</td>
<td>12.0±1.5, 67</td>
<td>19.5±4.0, 66</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Frequency of CRP measures, times</td>
<td>12±7</td>
<td>12±7</td>
<td>13±8</td>
<td>15±7</td>
<td>7±5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Methods of CRP measurements

- Turbidimetric immunoassay, n (%) 128/232 (56.2) 40/67 (59.7) 34/67 (50.7) 34/66 (51.5) 20/32 (62.5) 0.54
- Latex agglutination nephelometry, n (%) 104/232 (44.8) 27/67 (40.3) 33/67 (49.3) 32/66 (48.5) 12/32 (37.5) <0.0001

- Initial CRP, n, mg/dL 2.7±4.8, 232 1.2±2.0, 67 1.6±3.1, 67 2.9±4.6, 66 8.1±7.6, 32 0.11
- Age, n, y 64.1±11.9, 232 63.4±11.9, 67 62.4±12.1, 67 65.4±12.0, 66 66.3±11.0, 32 0.31
- Male sex, n (%) 165/232 (71.1) 45/67 (67.2) 48/67 (71.6) 53/66 (80.3) 19/32 (59.4) 0.15
- Time from onset to admission, d 1.1±2.3 0.6±1.1 0.5±0.9 0.5±0.9 4.7±4.3 <0.0001
- Overweight (BMI >25 kg/m²), n (%) 78/230 (33.9) 13/67 (19.4) 29/67 (43.3) 26/66 (39.4) 10/30 (33.3) 0.02
- Hypertension, n (%) 167/232 (72.0) 47/67 (70.1) 45/67 (67.2) 51/66 (77.3) 24/32 (75.0) 0.58
- Hyperlipidemia, n (%) 74/232 (31.9) 22/67 (32.8) 17/67 (25.4) 27/66 (40.9) 8/32 (25.0) 0.21
- Diabetes mellitus, n (%) 23/232 (9.9) 7/67 (10.4) 4/67 (6.0) 7/66 (10.6) 5/32 (15.6) 0.5
- Current smoking, n (%) 111/232 (47.8) 25/67 (37.3) 41/67 (61.2) 32/66 (48.5) 13/32 (40.4) 0.06
- Asthma, n (%) 8/232 (3.4) 2/67 (3.0) 1/67 (1.5) 4/66 (6.1) 1/32 (3.1) 0.54
- Marfan syndrome, n (%) 6/232 (2.6) 3/67 (4.5) 0/67 (0) 2/66 (3.0) 1/32 (3.1) 0.42
- Atrial fibrillation, n (%) 10/227 (4.4) 2/67 (3.0) 1/66 (1.5) 5/64 (7.8) 2/31 (6.5) 0.3
- Previous MI or angina pectoris, n (%) 19/232 (8.2) 5/67 (7.5) 3/67 (4.5) 8/66 (12.1) 3/32 (9.4) 0.44
- Previous aortic dissection, n (%) 3/232 (1.3) 0/67 (0) 0/67 (0) 3/66 (4.5) 0/32 (0) 0.05
- Aortilac aneurysm, n (%) 36/232 (15.5) 8/67 (11.9) 9/67 (13.4) 15/66 (22.7) 4/32 (12.5) 0.29
- Creatinine at admission, n, mg/dL 1.0±1.2, 232 1.1±1.7, 67 1.0±1.4, 67 1.1±0.7, 66 0.8±0.3, 32 0.11
- Creatinine at discharge, n, mg/dL 1.1±1.4, 225 1.0±1.0, 64 1.1±1.5, 67 1.4±1.9, 65 0.9±3.29 0.07
- Impaired renal function at admission, n (%) 63/232 (27.2) 13/67 (19.4) 14/67 (20.9) 27/66 (40.9) 9/32 (28.1) 0.02
- Impaired renal function at discharge, n (%) 73/225 (32.4) 18/64 (28.1) 17/67 (25.4) 28/65 (43.1) 10/29 (34.5) 0.14
- White blood cell counts (×10³/mm³), n 12.0±3.9, 232 2.4±3.7, 67 12.7±3.7, 67 0.0±4.0, 66 10.5±3.4, 32 <0.0001
- Surgery at initial hospitalization, n (%) 17/232 (7.3) 3/67 (4.5) 3/67 (4.5) 8/66 (12.1) 3/32 (9.4) 0.26
- CT findings
- Nonthrombosed type, n (%) 102/232 (44.0) 28/67 (41.8) 25/67 (37.3) 36/66 (54.5) 13/32 (40.6) 0.21
- Maximum aorta diameter, n, mm 39.0±8.0, 232 37.7±7.3, 67 38.2±6.8, 67 40.1±8.9, 66 40.9±9.3, 32 0.31
- DeBakey Ila (did not across diahragma), n/N (%) 45/232 (19.4) 16/67 (23.9) 14/67 (20.9) 10/66 (15.2) 5/32 (15.6) 0.57
- Systolic BP at admission, n, mm Hg 156±29, 232 156±25, 67 159±29, 67 155±33, 66 153±25, 32 0.65
- Diastolic BP at admission, n, mm Hg 84±18, 232 83±17, 67 88±17, 67 82±21, 66 85±14, 32 0.11
- Heart rate at admission, n, per min 82±16, 232 80±17, 67 81±18, 67 83±14, 66 87±17, 32 0.26
- Systolic BP at discharge, n, mm Hg 121±16, 232 119±15, 67 120±17, 67 122±19, 66 123±12, 32 0.53
- Diastolic BP at discharge, n, mm Hg 70±10, 232 70±9, 67 71±11, 67 68±9, 66 72±9, 32 0.13
- Heart rate at discharge, n, per min 67±12, 232 66±11, 67 63±10, 67 68±13, 66 73±15, 32 0.01

Data are expressed as mean±SD or percentage unless otherwise specified. χ² test was used for categorical variables. One-way ANOVA or Kruskal-Wallis test was used for continuous variables. BMI indicates body mass index; BP, blood pressure; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MI, myocardial infarction.

*No patient had fenestrating or stenting at initial hospitalization.
Variables HR 95% CI P

Peak CRP
Middle tertile (T2) of peak CRP (vs lowest tertile [T1]) 2.59 1.13 to 5.94 0.02
Highest tertile (T3) of peak CRP (vs lowest tertile [T1]) 5.13 2.26 to 11.62 <0.0001
Unavailable peak CRP group (UG) (vs lowest tertile [T1]) 7.07 2.60 to 19.26 0.0001

Initial CRP
Middle tertile of initial CRP (vs lowest tertile of initial CRP) 1.37 0.69 to 2.73 0.37
Highest tertile of initial CRP (vs lowest tertile of initial CRP) 1.14 0.57 to 2.30 0.71
Time from onset to admission 0.88 0.76 to 1.02 0.10
Overweight 0.92 0.51 to 1.65 0.78
Current smoking 1.09 0.63 to 1.90 0.76
Impaired renal function at admission (eGFR <60 mL/min) 1.22 0.67 to 2.21 0.51
White blood cell counts (×10^9/mm^3) 0.95 0.88 to 1.02 0.14
Heart rate at discharge (per 1/min incremental) 1.02 1.00 to 1.04 0.05
Diuretics 1.69 0.90 to 3.17 0.10

P values
Overall, <0.0001
T1 vs. T2, 0.09
T1 vs. T3, 0.0001
T1 vs. UG, 0.0004
T2 vs. T3, 0.01
T2 vs. UG, 0.06
T3 vs. UG, 0.63

19.26], P=0.0001; T3: HR: 5.13 [95% CI: 2.26 to 11.62], P<0.0001; T2: HR: 2.59 [95% CI: 1.13 to 5.94], P=0.02) even after controlling for all of the confounding factors. In this model, we also divided patients into 3 groups according to the tertiles of initial CRP levels. However, neither the highest tertile of initial CRP (versus the lowest tertile of initial CRP group: HR: 1.14 [95% CI: 0.57 to 2.30]; P=0.71) nor the middle tertile of initial CRP (versus the lowest tertile of initial CRP group: HR: 1.37 [95% CI: 0.69 to 2.73]; P=0.37) was a significant predictor of adverse events. In model 2, the tertiles of peak CRP and known variables such as age, sex, maximum aortic diameter, false lumen closure status, the extent of dissection (DeBakey IIIa or IIIb), impaired renal function, statins, calcium channel blockers, ß-blockers, and angiotensin-converting enzyme inhibitors at discharge were included as independent variables. The 2 different methods of CRP measurement at our institution were also included as independent variables. UG (HR: 4.28 [95% CI: 1.78 to 10.32]; P=0.001), T3 (HR: 3.99 [95% CI: 1.78 to 8.99]; P=0.0008), and T2 (HR: 2.42 [95% CI: 1.04 to 5.61]; P=0.04) were associated with adverse events in long-term follow-up (Table 3). In model 3, we adopted all of the independent variables used in model 1 and model 2. UG (HR: 7.45 [95% CI: 2.20 to 25.28]; P=0.001), T3 (HR: 6.02 [95% CI: 2.44 to 14.87]; P=0.0001), and T2 (HR: 3.25 [95% CI: 1.37 to 7.71]; P=0.01) were associated with adverse events (Table 4).

We performed a secondary analysis using cardiovascular deaths and aortic events as a secondary end point. In 65 total events, there were 11 deaths that were less associated with aortic dissection (cancer [n=4], pneumonia [n=3], emphysema [n=1], renal failure [n=1], nephritic syndrome [n=1], and hemorrhagic shock [n=1]). After excluding these deaths, multivariate Cox regression analysis revealed that the tertiles of peak CRP were still significantly associated with adverse events even after controlling for all of the variables used in model 3 (T2 versus T1: HR: 2.64 [95% CI: 1.00 to 6.98], P=0.05; T3 versus T1: HR:
Maximum aorta diameter (per 1-mm incremental) 1.01 0.98 to 1.05 0.41
Nonthrombosed type 1.24 0.69 to 2.22 0.47
DeBakey IIIa (vs IIIb) 0.90 0.40 to 2.04 0.80

Impaired renal function at discharge (eGFR <60 mL/min) 2.27 1.26 to 4.11 0.01
Turbidimetric immunoassay (vs latex agglutination nephelometry) 0.36 0.15 to 0.84 0.02

Statins at discharge 1.11 0.44 to 2.82 0.83
CCB at discharge 0.46 0.18 to 1.17 0.10

β-Blockers at discharge 1.01 0.52 to 1.96 0.98
ACE inhibitors at discharge 0.50 0.25 to 0.97 0.04

Table 4. Multivariate Cox Regression Analysis Predicting Death or Event: Model 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Peak CRP</td>
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<td></td>
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<tr>
<td>Middle tertile (T2) of peak CRP</td>
<td>3.25</td>
<td>1.37 to 7.71</td>
<td>0.01</td>
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<tr>
<td>(vs lowest tertile [T1])</td>
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<tr>
<td>Highest tertile (T3) of peak CRP</td>
<td>6.02</td>
<td>2.44 to 14.87</td>
<td>0.0001</td>
</tr>
<tr>
<td>(vs lowest tertile [T1])</td>
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</tr>
<tr>
<td>Unavailable peak CRP group (UG)</td>
<td>7.45</td>
<td>2.20 to 25.28</td>
<td>0.001</td>
</tr>
<tr>
<td>(vs lowest tertile [T1])</td>
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<tr>
<td>Initial CRP</td>
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<tr>
<td>Middle tertile of initial CRP</td>
<td>1.48</td>
<td>0.71 to 3.09</td>
<td>0.29</td>
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<tr>
<td>(vs lowest tertile of initial CRP)</td>
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<tr>
<td>Time from onset to admission</td>
<td>0.91</td>
<td>0.78 to 1.07</td>
<td>0.25</td>
</tr>
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<td>Overweight</td>
<td>0.80</td>
<td>0.41 to 1.53</td>
<td>0.49</td>
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<td>Current smoking</td>
<td>0.77</td>
<td>0.41 to 1.44</td>
<td>0.41</td>
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<tr>
<td>Impaired renal function at admission (eGFR &lt;60 mL/min)</td>
<td>0.44</td>
<td>0.18 to 1.07</td>
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<td>White blood cell counts (×10^3/µL)</td>
<td>0.95</td>
<td>0.87 to 1.03</td>
<td>0.20</td>
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<tr>
<td>Heart rate at discharge (per 1/min)</td>
<td>1.02</td>
<td>0.99 to 1.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.14</td>
<td>0.52 to 2.51</td>
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<tr>
<td>Age (per 10-y incremental)</td>
<td>1.08</td>
<td>0.80 to 1.46</td>
<td>0.62</td>
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<td>Male sex</td>
<td>2.06</td>
<td>0.96 to 4.43</td>
<td>0.06</td>
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<tr>
<td>Maximum aorta diameter (per 1-mm incremental)</td>
<td>1.03</td>
<td>1.00 to 1.07</td>
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<td>Nonthrombosed type</td>
<td>1.31</td>
<td>0.68 to 2.55</td>
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<td>DeBakey IIIa (vs IIIb)</td>
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<tr>
<td>Impaired renal function at discharge (eGFR &lt;60 mL/min)</td>
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<td>1.86 to 8.50</td>
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<td>Turbidimetric immunoassay (vs latex agglutination nephelometry)</td>
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<td>Statins at discharge</td>
<td>0.99</td>
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<td>CCB at discharge</td>
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<td>0.21 to 2.18</td>
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<td>β-Blockers at discharge</td>
<td>1.18</td>
<td>0.57 to 2.44</td>
<td>0.65</td>
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<tr>
<td>ACE inhibitors at discharge</td>
<td>0.45</td>
<td>0.21 to 0.94</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate. In this model, all of the variables used in model 1 and model 2 are adopted as independent variables. All of the variables are adjusted in 1 step.

Discussion

We investigated whether the peak CRP level has any prognostic value in predicting long-term outcomes in 232 type B AAD patients. Although initial CRP levels were not associated with adverse events, peak CPR levels were significantly associated with adverse events. Peak CRP levels were a better marker than initial CRP levels in the risk stratification of type B AAD patients. Because it takes several days to reach a peak CRP, initial CRP levels might not reflect the whole severity of aortic dissection. Our results showed that the peak CRP level was a strong predictor of long-term outcomes in type B AAD.

Although type A AAD is a life-threatening disease and needs emergent surgery, type B AAD is considered to be a relatively benign condition, with few cases requiring emer-
gent surgery during hospital admission. However, long-term outcomes of type B AAD are not necessarily better than that of type A AAD.\textsuperscript{2,3} Type B AAD is associated with a high mortality rate (\textapprox 20\% at 3 years\textsuperscript{4}) and a high morbidity rate (\textapprox 30\% morbidity at 2 years) in the long term.\textsuperscript{4,5} Therefore, identifying high-risk patients is of special clinical importance.

Earlier studies have identified long-term predictors of morbidity and mortality in type B AAD, including female sex, a history of previous aortic aneurysm, a history of atherosclerosis, and impaired renal function.\textsuperscript{3,10,20,22} In particular, multiple groups have reported that the maximum aortic diameter (\textapprox 40 mm) and false lumen closure status are long-term predictors in type B AAD.\textsuperscript{4,6–9} Some of these predictors, including sex, history of previous aneurysm, and history of atherosclerosis, may be more representative of a patient’s high-risk clinical background rather than the nature of the aortic dissection itself. On the other hand, false lumen closure status and the maximum aortic diameter may represent the nature of the aortic dissection for each individual patient. These parameters are relatively simply derived from a 2D CT. False lumen closure status is generally classified as 1 of 2 patterns (thrombosed and nonthrombosed) or 3 patterns (thrombosed, nonthrombosed, and partially thrombosed).\textsuperscript{4,6,8–9} Maximum aortic diameter is calculated from a cross-sectional image.\textsuperscript{4,6,8} However, the anatomy of the aortic dissection is often complex and is not necessarily consistent, even during the initial hospital stay.\textsuperscript{23–25} It may be difficult to estimate the whole nature of the AAD by these simple imaging parameters alone.

The possible explanation for why an elevated peak CRP level was associated with long-term adverse events may be several fold. In general, the peak CRP level is an excellent marker for the severity of a variety of acute illnesses. For instance, an elevated peak CRP level during hospitalization for an acute myocardial infarction has been reported to be an independent predictor of cardiac rupture, left ventricular aneurysmal formation, 1-year cardiac death, and left ventricular remodeling.\textsuperscript{17,18,26,27} Peak CRPs in acute myocardial infarction might reflect the myocardial damage and severity of myocardial infarction itself in the acute phase. In our study, peak CRP levels are presumably reflective of the severity of AAD in the acute phase. Our results also suggest the possibility that the severity expressed by the peak CRP has a lasting impact on long-term clinical events.

Another possible explanation is that the peak CRP may represent the extent of the inflammatory reaction in the dissected aortic wall and may also reflect the damage to the lesion. Recent studies have revealed the close relationship between local inflammation in the aortic wall and the aortic dissection.\textsuperscript{10,12,28} Kuehl et al\textsuperscript{10} have demonstrated the association of inflammation with aortic dissection using positron emission tomography. He et al\textsuperscript{29} have immunopathologically demonstrated that T lymphocytes and macrophages are common features in medial degeneration in the aortic dissection. These studies suggest that inflammation is present in the dissected aortic wall. The severely damaged aortic wall may more easily expand, may be more prone to redissection, and may be at higher risk of rupture during the chronic phase versus a less severely damaged aortic wall.

The major part of CRP is synthesized by hepatocytes, driven by interleukin 6 with synergistic enhancement of interleukin 1 or tumor necrosis factor.\textsuperscript{29,30} CRP can also be produced locally in atherosclerotic lesions.\textsuperscript{31} Although CRP is generally considered to be an inflammatory marker or an atherosclerotic marker,\textsuperscript{32–34} CRP also plays a role as a mediator of atherosclerosis. CRP directly influences several phases of atherosclerosis via complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation, and thrombosis.\textsuperscript{31,35} Therefore, exaggerated CRP itself might exert harmful effects that promote the atherosclerosis of the dissected aortic wall.

Of the 232 study patients, there were 32 patients whose peak CRP was unavailable. Interestingly, the outcomes of these patients were comparable to the highest tertile of the peak CRP group. One possible explanation is the difference in “time from onset to admission.” The mean time from onset to admission in these 32 patients was 4.7 ± 4.3 days, which was longer than the other 3 groups. Some of these patients might not have received adequate medical therapy, such as aggressive blood pressure lowering in the days after the onset of dissection. Another possible explanation is a selection bias before admission to our medical center. Because our medical center is a tertiary referral hospital, patients who had developed complications over the course of several days may have subsequently been referred to our hospital.

Peak CRP as a long-term predictor has several advantages over other predictors. First, the predictive power is potent with a high HR (3.99 to 6.02 adjusted for all of the confounders) in the highest tertile of peak CRP levels. Even the middle tertile of peak CRP has a moderate HR (2.42 to 3.25). In addition, CRP is a relatively simple marker widely available for clinical use.

### Study Limitations

Although our study population is fairly large and the follow-up period is relatively long, this single-center retrospective study design poses a risk for patient selection bias. Because the timeline of the study period is fairly long, the change in the standard of care might have been a confounder of this study. Because CRP is a nonspecific inflammatory marker, it reflects not only the aortic dissection itself but also secondary processes, such as pneumonia. In addition, initial management, such as blood pressure control or pain control, might also affect the CRP. Although the CRP level was measured daily or every other day in most patients, it was measured less frequently in some patients. The methods to measure CRP have also changed from turbidimetric immunoassay to latex agglutination nephelometry during the study period. Although these 2 methods have been reported to be highly associated (\textit{r} = 0.9916; mean difference 0.19 mg/L; limits of agreement: –0.36 to 0.74 mg/L),\textsuperscript{36} latex agglutination nephelometry was a more accurate method.

However, the accuracy of the latex agglutination nephelometry is more important in detecting chronic inflammation in the general population and does not have as much significance during acute illness, whereas CRP levels are naturally much higher. Therefore, we do not think that changing the
method of CRP measurement would have a significant effect on our results. Because the time from onset to admission was different in each patient, the time from onset to initial CRP measurement after admission was also different in each patient. This time difference might limit the value of initial CRP. Our main diagnostic tool for the AAD has been CT with contrast. Therefore, it is often difficult to differentiate intramural hematoma from thomboosed type A AAD. In addition, we could not evaluate the presence of rapid aortic expansion as a study end point, because each interval between follow-up CT analyses was not consistent. However, our institution recommended elective surgery to patients who had rapid aortic expansion. Therefore, it is possible that we were able to capture rapid aortic expansion in a portion of patients. Finally, because the surgeons had access to laboratory values reflecting an increased inflammatory status during the index admission, there is a possibility that such information affected their decision to operate during long-term follow-up.

Perspectives

In our retrospective study, the peak CRP is a strong predictor for adverse long-term events in patients with type B AAD, but this should be validated by a prospective study. Peak CRP would be a better prognostic marker than an initial CRP. Obtaining an initial CRP level at 1 time point might be insufficient to identify high-risk patients. Our results may support the effort to find a peak CRP level for the risk stratification of type B AAD. Careful clinical follow-up may be warranted in those patients who have a high peak CRP during their index admission.

Disclosures

None.

References


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Running title; Peak CRP in type B aortic dissection

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263 patients with type B AAD was admitted

10 patients excluded due to lack of critical data such as CT.

253 patients was included in the study cohort

9 patients died during index admission

244 patients discharged from index admission

12 patients were lost to follow-up

232 patients was final study cohort

Peak CRP was available?

Yes

200 patients were divided according to tertile of peak CRP

Lowest tertile 0.60-9.37 mg/dl

67 patients as T1

Middle tertile 9.61-14.87 mg/dl

67 patients as T2

Highest tertile 14.90-32.60 mg/dl

66 patients as T3

No

Unavailable peak

32 patients as unavailable group (UG)
<table>
<thead>
<tr>
<th>Table S1. Each event among tertiles of peak CRP</th>
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<td>Low tertile of peak CRP (T1)</td>
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<td>Total event 12 (death 9 and event 3) N</td>
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<td>Deaths</td>
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