Predictive value of neutrophil to lymphocyte ratio for the presence of coronary artery ectasia in patients with aortic aneurysms

Hiroki Ikenaga, Satoshi Kurisu, Noriaki Watanabe, Takashi Shimonaga, Tadanao Higaki, Toshitaka Iwasaki, Hiroto Utsunomiya, Naoya Mitsuwa, Ken Ishibashi, Yoshihiro Dohi, Yukihiro Fukuda, Katsuhiko Imai, Taijiro Sueda, Yasuki Khara

Aortic aneurysms and coronary artery ectasia (CAE) frequently coexist and are associated with more pronounced inflammation. Neutrophil to lymphocyte ratio (NL ratio) is widely used as a marker of inflammation. However, the relation between CAE and NL ratio in patients with aortic aneurysms is not fully understood. This study was undertaken to assess the relation between CAE and NL ratio in patients with aortic aneurysms.

Methods: This study consisted of 93 consecutive patients with aortic aneurysms (AA group) and 79 patients without aortic aneurysms who had angiographically normal coronary arteries as the control group. Moreover, patients with aortic aneurysms were classified into two groups based on the presence of CAE: CAE (+) group (n = 44) and CAE (−) group (n = 49). We compared blood chemical parameters in both groups.

Results: In the AA group, 44 patients (47.3%) had CAE. The AA group had a significantly higher NL ratio than the control group (2.93 ± 1.43 vs. 2.45 ± 1.05, p = 0.027). Furthermore, the CAE (+) group had a significantly higher NL ratio than the CAE (−) group (3.39 ± 1.67 vs. 2.52 ± 1.04, p < 0.01). Multivariate logistic regression analysis revealed that the high NL ratio was an independent predictor for CAE in patients with aortic aneurysms (odds ratio 1.76, 95% confidence interval 1.24–2.69, p = 0.001).

Conclusions: Patients with aortic aneurysms had a significantly higher NL ratio than those without aortic aneurysms. Furthermore, the NL ratio might predict the presence of CAE in patients with aortic aneurysms.

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1. Introduction

Aortic aneurysms are an important cardiovascular disease and a complex disease with both genetic and environmental factors contributing to the disease process. In practice, established risk factors for aortic aneurysms include advancing age, male gender, smoking, hypertension and atherosclerosis [1]. In addition, aortic aneurysms are associated with more pronounced inflammation and elevation of inflammatory markers in patients with aortic aneurysms is widely recognized [2]. Also, coronary artery disease is the most important cause of morbidity and mortality in patients with aortic aneurysms, including during the postoperative period of aortic aneurysms [3]. However, it is difficult to predict morbidity and mortality only by evaluating coronary artery stenosis [4]. On the other hand, it was reported that coronary artery ectasia (CAE) was frequently observed in patients with aortic aneurysms [5,6] and CAE regardless of aortic aneurysms may be a form of atherosclerosis with more active inflammatory [7–11]. White blood cell (WBC) count and related parameters are markers of inflammation in cardiovascular disease [12,13]. Especially, neutrophil to lymphocyte ratio (NL ratio) has been shown to have the greatest predictive value for poor outcomes in patients with coronary artery disease [13]. However, the relation between CAE and NL ratio in patients with aortic aneurysms is not fully understood. This study was undertaken to assess the relation between CAE and NL ratio in patients with aortic aneurysms.

2. Methods

2.1. Study patient

In total, 1735 patients underwent coronary angiograms from January 2011 to October 2013 at Hiroshima University Graduate School of Biomedical and Health Sciences. Of these, we excluded patients accompanied with acute coronary syndrome and chronic inflammatory disease. In addition, we excluded patients with traumatic,
inflammatory, infective and congenital aortic aneurysms. We have retrospectively analyzed 93 consecutive patients with aortic aneurysms (AA group) and 79 patients without aortic aneurysms who had angiographically normal coronary arteries and no ischemia on myocardial perfusion scintigram or the treadmill exercise test as the control group (control group). Moreover, patients with aortic aneurysms were classified into two groups based on the presence of CAE; CAE (+) group (n = 44) and CAE (−) group (n = 49). Coronary angiograms were performed due to the presence of anginal chest pain or the evaluation of coronary artery before aortic aneurysm surgery. Angiographically normal coronary arteries were defined as no reduction of the internal diameter of the coronary arteries. Aortic aneurysms were defined as a circumferential or local enlargement (the diameter was increased to a degree at least 1.5-fold greater than normal (exceeding 45 mm in the thoracic region and 30 mm in the abdominal region)) or protrusion of a part of the aortic wall [14,15]. The maximum minor-axis diameter was used in principle for plain and early contrast-enhanced computed tomography images [16]. Estimated glomerular filtration rate (eGFR) was calculated using the Japanese equations from serum creatinine, and chronic kidney disease (CKD) was thought to be present if it was <60 ml/min per 1.73 m². Informed consent was obtained from each patient. This study was approved by the ethical committee at Hiroshima University Graduate School of Biomedical and Health Sciences.

2.1. Inclusion criteria

- Patients with aortic aneurysms (AA group) and 79 patients with normal coronary arteries and no ischemia on myocardial perfusion scintigram (control group).

2.2. Laboratory measurements

Blood samples were collected from the ante-cubital vein by an atraumatic puncture just before the coronary angiography in the postabsorptive state and were sent to the central laboratory of our hospital within 1 h after collection. Venous blood was collected in a tube containing K3 EDTA for the measurement of hematologic indices in all patients. Hematologic indices were evaluated from a complete blood count analysis performed at the central laboratory of our hospital.

2.3. Angiographic evaluation

Coronary angiograms were obtained and evaluated according to standard techniques using 4 Fr catheter. Using quantitative coronary angiographic (QCA) analysis (QCA-CMS v.6.0, Medis, Leiden, NL), coronary artery stenosis was defined as the 50% reduction of the internal diameter of the coronary arteries compared to normal, non-ectatic segments. Coronary artery disease (CAD) severity was assessed by the number of diseased vessels [the right coronary artery (RCA), left anterior descending (LAD), or left circumflex (LCX) coronary artery]. The left main coronary artery (LMCA) was considered a two-vessel disease. Coronary artery ectasia (CAE) was defined as coronary artery with the diameter of the ectatic segment being more than 1.5-fold larger compared with an adjacent healthy reference segment [17,18].

Table 1: Baseline characteristics between the patients with AA and those without AA.

| Clinical characteristics                  | AA group (n = 93) | Control group (n = 79) | p value |
|-------------------------------------------|------------------|-----------------------|--------|
| Age (years)                               | 72.8 ± 8.8       | 67.1 ± 10.9           | <0.001 |
| Male                                      | 75 (80.7%)       | 55 (69.6%)            | 0.09   |
| Hypertension                              | 77 (82.8%)       | 55 (69.6%)            | 0.04   |
| Dyslipidemia                              | 41 (44.1%)       | 41 (51.9%)            | 0.31   |
| Diabetes mellitus                         | 17 (18.3%)       | 28 (35.4%)            | 0.01   |
| Current smoker                            | 28 (30.1%)       | 23 (29.1%)            | 0.87   |
| Body mass index (kg/m²)                   | 23.4 ± 4.0       | 24.1 ± 3.7            | 0.28   |
| Previous MI                               | 6 (6.5%)         | 0 (0%)                | 0.02   |
| Atrial fibrillation                       | 9 (9.7%)         | 5 (6.3%)              | 0.42   |
| Medication                                |                  |                       |        |
| Aspirin                                   | 28 (30.1%)       | 19 (24.1%)            | 0.37   |
| β-Blocker                                 | 28 (30.1%)       | 16 (20.3%)            | 0.13   |
| ACE-I/ARB                                 | 51 (54.8%)       | 41 (51.9%)            | 0.70   |
| ACE-I/ARB                                 | 56 (60.2%)       | 36 (45.6%)            | 0.06   |
| Statin                                    | 28 (30.1%)       | 23 (29.1%)            | 0.43   |
| Diuretic                                  | 11 (11.8%)       | 12 (15.2%)            | 0.52   |
| LV EF (%)                                 | 60.4 ± 7.8       | 61.7 ± 7.2            | 0.16   |

| Laboratory data                           |                  |                       |        |
| White blood cell (10³/µl)                 | 6721 ± 2258      | 6396 ± 2121           | 0.30   |
| Nt ratio                                  | 2.93 ± 1.43      | 2.45 ± 1.05           | 0.027  |
| Hemoglobin (g/dl)                         | 12.95 ± 2.07     | 13.42 ± 1.90          | 0.11   |
| Hematocrit (%)                            | 38.33 ± 5.70     | 39.58 ± 5.11          | 0.13   |
| C-reactive protein (mg/dl)                | 1.03 ± 2.97      | 0.19 ± 0.29           | <0.01  |
| Platelet (mm³/µl)                         | 187.30 ± 62.28   | 200.29 ± 66.37        | 0.48   |
| eGFR (ml/min per 1.73 m²)                 | 61.02 ± 22.78    | 65.80 ± 28.74         | 0.08   |
| eGFR < 60 ml/min per 1.73 m²              | 41 (44.1%)       | 28 (35.4%)            | 0.25   |
| HDL cholesterol (mg/dl)                   | 50.9 ± 14.3      | 57.6 ± 22.2           | 0.054  |
| LDL cholesterol (mg/dl)                   | 110.4 ± 28.9     | 110.1 ± 44.1          | 0.40   |
| Triglyceride (mg/dl)                      | 133.9 ± 64.1     | 147.2 ± 127.9         | 0.78   |
| HDL A1c (%)                               | 5.92 ± 0.52      | 6.24 ± 1.45           | 0.63   |
| D-dimer (µg/ml)                           | 6.73 ± 7.67      | 1.03 ± 1.59           | <0.01  |

3. Results

In the AA group, there were 30 (32.3%) patients with ascending thoracic aneurysms and 63 (67.7%) patients with descending thoracic or abdominal aneurysms. The baseline characteristics of the study patients are shown in Table 1. Age, the frequencies of hypertension and previous myocardial infarction (MI) were significantly higher in the AA group than in the control group (age; 72.8 ± 8.8 years vs. 67.1 ± 10.9 years, p = 0.001, hypertension; 82.8% vs. 69.6%, p = 0.04, previous MI; 6.5% vs. 0%, p = 0.02, respectively). The frequencies of diabetes mellitus was significantly lower in the AA group than in the control group (18.3% vs. 35.4%, p = 0.01). There was no significant difference in other baseline clinical variables between the AA group and the control group. The AA group had a significantly higher C-reactive protein level and D-dimer level than the control group (C-reactive protein; 1.03 ± 2.97 mg/dl vs. 0.19 ± 0.29 mg/dl, p < 0.01, D-dimer; 6.73 ± 7.67 µg/ml vs. 1.03 ± 1.59 µg/ml, p < 0.01, respectively). The AA group had a significantly higher NL ratio than the control group (2.93 ± 1.43 vs. 2.45 ± 1.05, p = 0.027). There was no significant difference in other blood chemical parameters between the AA group and the control group.

Angiographic characteristics of the study patients are shown in Table 2. Forty-three of 93 patients (46.2%) in the AA group had a significant coronary artery stenosis. In the AA group, the prevalence of coronary artery stenosis and CAD severity were significantly higher in the patients with descending thoracic or abdominal aneurysms than those with ascending thoracic aneurysms.
and protein, LDL; low-density lipoprotein, HbA1c; hemoglobin A1c. P values were two-tailed, with a significance level of 0.05.

Coronary stenosis 43 (46.2%), LMCA stenosis 8 (8.6%), LAD stenosis 16 (17.2%), LCX stenosis 13 (14.0%), RCA stenosis 26 (28.0%).

CAD severity:
- 1-Vessel disease: 25 (26.9%)
- 2-Vessel disease: 11 (11.9%)
- 3-Vessel disease: 7 (7.3%)

Coronary ectasia:
- LAD ectasia: 44 (47.3%)
- Diffuse: 17 (18.5%)
- LCX ectasia: 24 (26.1%)
- Diffuse: 21 (22.8%)
- RCA ectasia: 32 (34.8%)
- Diffuse: 29 (31.5%)

LMCA = left main coronary artery, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, RCA = right coronary artery, CAD = coronary artery disease.

with ascending thoracic aneurysms (coronary artery stenosis: 55.5% vs. 26.7%, p < 0.01, CAD severity: 1-/2-/3-vessel disease: 30.1/14.3/11.1% vs. 20.0/6.7/0%, p < 0.02). Forty-four of 93 patients (47.6%) in the AA group had CAE. The prevalence of CAE in the AA group was 32.6% in LAD, 26.1% in the LCX and 34.8% in RCA in the AA group. Also, in each ectatic artery, the prevalence of diffuse CAE was 56.6% in LAD, 87.5% in LCX and 90.6% in RCA.

The baseline characteristics between the CAE (+) group and the CAE (−) group are shown in Table 3. There was no significant difference in the ratio of ascending thoracic aneurysms. Prescription of β-blocker was significantly higher in the CAE (+) group than in the CAE (−) group (40.9% vs. 20.4%, p = 0.03). There was no significant difference in other baseline clinical variables between the CAE (+) group and the CAE (−) group. The CAE (+) group had a significantly higher WBC level and triglyceride level than the CAE (−) group (WBC: 7149 ± 19371 μl/μl vs. 6338 ± 24691 μl/μl, p = 0.04, triglyceride: 147.4 ± 61.4 mg/dl vs. 121.7 ± 64.6 mg/dl, p = 0.02, respectively). Relation between NL ratio and CAE in patients with aortic aneurysms is shown in Fig. 1. The CAE (+) group had a significantly higher NL ratio than the CAE (−) group (3.39 ± 1.67 vs. 2.52 ± 1.04, p < 0.01). Univariate and multivariate logistic regression analyses to identify independent predictors of the presence of CAE in patients with aortic aneurysms are shown in Table 4. Univariate analysis revealed that the NL ratio and triglyceride were associated with CAE in patients with aortic aneurysms (NL ratio; odds ratio [OR] 1.65, 95% confidence interval [CI] 1.18–2.44, p = 0.002, triglyceride; OR 1.01, 95% CI 1.01–1.02, p = 0.049, respectively). To detect the independent effect of the NL ratio for the presence of CAE in patients with aortic aneurysms, the NL ratio as well as triglyceride and high-density lipoprotein cholesterol was incorporated to multivariate logistic regression analysis. Multivariate logistic regression analysis revealed that the high NL ratio was an independent predictor for CAE in patients with aortic aneurysms (OR 1.76, 95% CI 1.24–2.69, p = 0.001). Logistic regression analysis of the NL ratio for CAE after adjustment for propensity scores is shown in Table 4. After adjusting for ascending thoracic aneurysms, age, male, hypertension, dyslipidemia, diabetes mellitus, current smoker, body mass index, previous MI, atrial fibrillation, left ventricular ejection fraction, use of aspirin, β-blocker, Ca-blocker, angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARB), statin and diuretic using propensity scores, the NL ratio was an independent predictor for CAE in patients with aortic aneurysms (OR 1.56, 95% CI 1.10–2.40, p = 0.01).

### 4. Discussion

The major finding of the present study was that patients with aortic aneurysms had a significantly higher NL ratio than those without aortic aneurysms. Furthermore, among the AA group, patients with CAE had a significantly higher NL ratio than those without CAE and the high NL ratio might predict the presence of CAE. To our knowledge, this is the first report to show that the NL ratio is an independent predictor of CAE in patients with aortic aneurysms. This finding suggests that the NL ratio may be a useful biomarker for the prediction of CAE in patients with aortic aneurysms.
first report to present a relation between NL ratio and CAE in patients with aortic aneurysms.

Previous studies have shown that there are some differences in the pathobiology between descending thoracic or abdominal aortic aneurysms and ascending thoracic aneurysms [19,20]. Descending thoracic or abdominal aortic aneurysms are characterized by a decrease in the number of smooth muscle cells in the aortic media layer and fragmentation of the extracellular matrix of the aorta at the site of the aneurysms because of inflammation, tissue remodeling and upregulation of matrix metalloproteinases (MMPs) [21]. Ascending thoracic aneurysms are characterized by medial necrosis, mucoid infiltration, cyst formation with elastin degradation and vascular smooth muscle cell apoptosis [19]. Although there are some differences in the pathobiology between descending thoracic or abdominal aortic aneurysms and ascending thoracic aneurysms, inflammatory response has an influence on the formation of aortic aneurysms [22]. In the present study, the AA group had a significantly higher WBC level and NL ratio than the control group. It was suggested that the inflammatory response was stronger in the CAE (+) group than in the CAE (−) group and this may eventually lead to a high WBC level and NL ratio in the CAE (+) group.

Patients with CAE present poor long-term cardiac outcomes [28]. CAE has been shown to decrease coronary flow velocity [29]. In addition, the extent of CAE was correlated with coronary flow velocity and associated with a history of myocardial infarction independent of coexisting significant coronary stenosis [28]. And persistent slow coronary blood flow is associated with an increased risk of stent thrombosis [30]. It was reported that preoperative NL ratio appears to be a significant predictor of both 30-day mortality and long-term outcome in open aortic aneurysm surgery and myocardial infarction was the main cause of perioperative mortality for aortic aneurysms [31]. For these reasons, it has a clinical importance to assess NL ratio and detect CAE in patients with aortic aneurysms in clinical decisions regarding management of these patients to avoid myocardial infarction and stent thrombosis. Also, it was reported that ACE-I, ARB and statin reduced MMPs and significantly inhibited infiltration of macrophages into the aortic wall, accompanied by a reduction of protein expression of intercellular adhesion molecule-1 [32–34]. Because these drugs reduce systemic inflammation, more use of these drugs would be an attractive strategy as medical treatment to prevent progression to CAE and cardiovascular event in patients with a high NL ratio before aortic aneurysm surgery.

5. Study limitations

Major limitation of this study is a small sample size. In addition, this study is a retrospective analysis. Accurate assessment of coronary artery stenosis may be difficult in the presence of coronary ectasia due to uncertainty in identifying the reference part of the vessel. Cytokines related to inflammation were not investigated. We did not perform an analysis of the prognostic value of the NL ratio in CAE. Although the formation of aortic aneurysms and CAE is a slow, chronic condition, we only evaluated a single NL ratio in this study.

6. Conclusions

The presence of aortic aneurysms was associated with a higher incidence of angiographic CAE and high NL ratio. Furthermore, the NL ratio might predict the presence of CAE in patients with aortic aneurysms. These findings suggested that CAE might need to be evaluated in patients with both aortic aneurysms and high NL ratio. Further studies should be advocated to investigate the more clinical prognostic value of NL ratio for patients with aortic aneurysms to reduce cardiovascular event and long-term outcome of patients with both aortic aneurysms and NL ratio.

Conflict of interest

None declared.

Acknowledgments

None.
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