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# Associations between inflammatory markers and all-cause mortality in the general population: the Nagahama study.

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Received July 9, 2025; accepted July 28, 2025
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## ABSTRACT

**Background:** Inflammatory markers, especially C-reactive protein (CRP), have been reported to be associated with all-cause mortality. In addition, α1-antitrypsin and white blood cell (WBC)-based inflammatory markers were suggested to represent mortality risk. We aimed to investigate whether simultaneous assessment of these markers was more useful for evaluating mortality risk than compared to individual assessment.
**Methods:** This longitudinal study included 5,970 Japanese community residents (mean age 62.9 years). Circulating levels of inflammatory markers were measured from baseline blood samples. All-cause mortality was ascertained by referring to the residential records.
**Results:** During a mean follow-up duration of 13.5 years, 550 deaths occurred. Kaplan–Meier curves for mortality showed significant differences across the quintiles of each marker (log-rank test: $P < 0.05$). Results of the Cox proportional hazard model adjusted for potential covariates indicated that α 1-antitrypsin (fifth quintile: hazard ratio 1.73, $P < 0.001$) and CRP (fourth quintile: hazard ratio 1.49, $P = 0.001$; fifth quintile: hazard ratio 1.33, $P = 0.068$) were significantly associated with mortality. Among the WBC-based markers, platelet-to-lymphocyte ratio (hazard ratio 1.38, $P = 0.002$), systemic immune–inflammation index (hazard ratio 1.27, $P = 0.014$), and lymphocyte-to-monocyte ratio (hazard ratio 1.39, $P = 0.035$) showed significant associations. When these markers were included in the same model, α1-antitrypsin, but not CRP, showed pronounced association, whereas the WBC-based markers showed significant but weak associations.
**Conclusions:** α1-antitrypsin was identified as a good marker for long-term mortality risk assessment in the general population. Combining these markers might help identify high risk populations.
〔Lab Med Int 2025; 4(4): 105-113〕

**Key Words**
white blood cell count, α1-antitrypsin, C-reactive protein, all-cause mortality, general population

## I. Introduction

Systemic inflammation is exaggerated in patients with cardiovascular diseases [1)2)] and cancers [2)]. Among several peripheral blood markers for systemic inflammation, high-sensitivity C-reactive protein (hsCRP) is a well-investigated marker for indicating increased risk of cardiovascular [3)] and all-cause mortalities [4)-7)]. hsCRP

is an acute-phase reactant, the production of which is stimulated by interleukin-6 released from activated immune cells [1]. A previous report revealed that hsCRP was associated with all-cause mortality in a general Japanese population aged 50 years or over [8]. α1-antitrypsin (AAT), another acute-phase inflammatory marker, has also been reported to be associated with cardiovascular disease events [9)-13)] and all-cause mortality [8] in general populations. AAT is a major serine protease inhibitor with broad-spectrum anti-inflammatory, immunomodulatory, and anti-infective tissue-repair functions [14]. In addition, several markers based on white blood cell (WBC) counts, such as neutrophil-to-lymphocyte ratio (NLR), have been suggested to indicate systemic inflammation and reported to be associated with the prognosis of certain cancers [15)-16)], sepsis [18], and stroke [19]. NLR has also been reported to be associated with the severity of coronary artery disease patients [20]. Other WBC-based markers, including platelet-to-lymphocyte ratio (PLR), systemic immune–inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR), have also been suggested to be associated with a worse prognosis in cancer patients [21)-23)]. Even in a general population, NLR, PLR, SII, and LMR were suggested to be associated with all-cause mortality [24)-28)].

Therefore, we hypothesized that the simultaneous assessment of conventional and WBC-based inflammatory markers may be more useful for mortality risk evaluation than individual assessment. Furthermore, previous findings on WBC-based markers have been focused on Western populations [24)-26)28)], with limited results in Asian populations [27)29)]. To our knowledge, no reports have been published on Japanese cohorts. We aimed to investigate this hypothesis by the analysis of large-scale longitudinal study of a general Japanese population.

## II. Methods

### *Study population*

We analyzed the data of the Nagahama Study [8)30)], an ongoing longitudinal study based on community residents of Nagahama City, Japan, located in central Japan with approximately 113,000 inhabitants in 2024. Participants of the Nagahama Study were recruited at a baseline survey performed between 2008 and 2010. Nagahama City residents aged 30–86 years who were living independently without physical impairment or dysfunction were eligible to participate. Of the baseline population (N = 9,764), 5,970 were ultimately included in this study after excluding participants who met the following exclusion criteria; younger than 50 years (N = 3,736), using hemodialysis therapy (N = 4), pacemaker implantation (N = 11), having clinical values widely deviated from their distributions [platelet count ≥ 550 × $10^9$/L (N = 1), NLR ≥ 9 (N = 5), gamma-glutamyl transferase (γGT) ≥ 500 IU/L (N = 10), ALT ≥ 200 IU/L (N = 2)], and incomplete measurement of required clinical values (N = 25).

All procedures were approved by the Ethics Committee of Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.

### *All-cause mortality*

All-cause mortality was identified by reviewing residential registry records managed by the Nagahama City Office. Participants who had relocated out of Nagahama City were censored. Follow-up period was calculated from participation in the baseline survey to the date of relocation, death or to current end of the follow-up period (March 31, 2024).

### *Inflammatory markers*

Serum levels of AAT and hsCRP were measured using a blood sample drawn at baseline in a commercial laboratory (SRL Inc., Tokyo, Japan) using the N-antiserum to Human Alpha-1-Antitrypsin Kit or N-Latex CRP II Kit (Siemens Healthcare Diagnostics, Munich, Germany). Other blood markers were measured using the same sera in another commercial laboratory (Medic Inc., Shiga, Japan). Blood cell counts and blood cell fractions were measured using an automated hematology analyzer (Sysmex XE–2100, Sysmex Corporation, Kobe, Japan) using the blood specimens drawn at baseline. NLR, PLR, SII, and LMR were calculated using the following formulas:

NLR = neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

SII = (neutrophil count × platelet count)/lymphocyte count

LMR = lymphocyte count/monocyte count

### *Basic clinical parameters*

Other clinical parameters used in this study were obtained at baseline. Data on histories of cancers and cardiovascular diseases, medication use, and smoking and drinking habits were obtained using a structured questionnaire. Heavy drinking was defined as consuming ≥ 2 Go (men) or ≥ 1 Go (women) of alcohol per sitting. Go is a Japanese traditional liquor unit that corresponds to 22 g of ethanol. Blood pressure was measured twice after a few minutes of rest in a sitting position using a cuff-oscillometric device (HEM-9000AI; Omron Healthcare,

Kyoto, Japan). The mean of two readings was used as the representative value.

### *Statistical analysis*

Values were expressed as means ± standard deviations, medians and interquartile ranges, or frequencies. The Student's t-test, analysis of variances, Mann–Whitney U test and Kruskal–Wallis test were used to assess group differences in numerical variables, whereas chi-squared tests were used to assess frequency differences. Spearman's rank correlation coefficient was used to examine correlations among numerical variables. Mortality rate was calculated per 10,000 person-years. Survival curves across quintiles of inflammatory markers were depicted using the Kaplan–Meier method, and group differences in the survival curves were assessed using the log-rank test.

We first used Cox proportional hazards models to identify factors independently associated with all-cause mortality. Each model included quintiles of one WBC-based marker and was adjusted for standard covariates, including age, sex, body mass index, current smoking, heavy drinking, history of cancer, history of cardiovascular disease, mean blood pressure, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipo-

**Table 1** Baseline clinical characteristics of the study participants (N = 5,970)

| | Alive N = 5,420 | Died N = 550 | P |
|---|---|---|---|
| Age, years old | 62.4 ± 6.3 | 67.1 ± 5.6 | <0.001 |
| Sex male % | 32.9 | 60.4 | <0.001 |
| Body mass index, kg/m2 | 22.7 ± 3.0 | 22.8 ± 3.2 | 0.475 |
| Current smoking, % | 10.2 | 19.6 | < 0.001 |
| Heavy drinking, % | 6.4 | 8.7 | 0.038 |
| History of cancers, % | 5.8 | 10.6 | < 0.001 |
| History of cardiovascular diseases, % | 3.6 | 9.1 | < 0.001 |
| Systolic blood pressure, mmHg | 128 ± 17 | 132 ± 18 | < 0.001 |
| Diastolic blood pressure, mmHg | 78 ± 11 | 79 ± 11 | < 0.001 |
| ***Plasma markers*** | | | |
| Hemoglobin A1c, % | 5.6 ± 0.5 | 5.7 ± 0.8 | < 0.001 |
| High-density lipoprotein cholesterol, mg/dL | 65 ± 17 | 60 ± 17 | < 0.001 |
| Low-density lipoprotein cholesterol, mg/dL | 129 ± 30 | 122 ± 32 | < 0.001 |
| Albumin, g/dL | 4.4 ± 0.2 | 4.4 ± 0.2 | < 0.001 |
| Creatinine, mg/dL | 0.7 [0.6–0.8] | 0.8 [0.6–0.9] | < 0.001 |
| Alanine aminotransferase, IU/L | 19 [15–25] | 19 [15–26] | 0.908 |
| Gamma-glutamyl transferase, IU/L | 23 [16–36] | 27 [19–43] | < 0.001 |
| High-sensitivity C-reactive protein, μ g/mL | 0.34 [0.17–0.69] | 0.47 [0.22–0.93] | < 0.001 |
| α1-antitrypsin, mg/dL | 131 ± 18 | 140 ± 23 | < 0.001 |
| ***Blood cell counts*** | | | |
| White blood cells, × $10^9$ /L | 5.8 ± 1.4 | 6.1 ± 1.7 | < 0.001 |
| Neutrophils, × $10^9$ /L | 3.3 ± 1.0 | 3.5 ± 1.2 | < 0.001 |
| Lymphocytes, × $10^9$ /L | 2.0 ± 0.6 | 2.1 ± 0.7 | 0.840 |
| Monocytes, × $10^9$ /L | 0.3 ± 0.1 | 0.3 ± 0.1 | < 0.001 |
| Platelet counts, × $10^9$ /L | 226 ± 49 | 223 ± 57 | 0.194 |
| ***White blood cell-based inflammatory markers*** | | | |
| NLR | 1.68 ± 0.72 | 1.86 ± 0.85 | < 0.001 |
| PLR | 117 ± 38 | 118 ± 48 | 0.485 |
| SII | 381 ± 189 | 418 ± 240 | < 0.001 |
| LMR | 7.93 ± 2.84 | 6.99 ± 2.62 | < 0.001 |

Values are mean ± standard deviation, median and interquartile range, or frequency. Statistical significance was assessed by the analysis of variance or the Chi-squared test. Cardiovascular diseases include symptomatic stroke, angina pectoris, and myocardial infarction. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; LMR, lymphocyte-to-monocyte ratio.

protein cholesterol, creatinine, albumin, alanine aminotransferase, and gamma-glutamyl transferase. Based on the results of these initial analyses, we then conducted Cox proportional hazards models that included the most abnormal quintiles of the statistically significant WBC-based markers, in order to evaluate their associations after further adjustment for serum inflammatory markers. The inflammatory markers included in this analysis were the fifth quintile (Q5) of AAT and a high hsCRP group, defined as either the fourth (Q4) or fifth (Q5) quintile. Finally, to provide clinically interpretable results, we conducted additional Cox proportional hazards analyses combining the high levels of these statistically significant inflammatory and WBC-based markers without adjusting for other covariates, in order to calculate crude hazard ratios. To account for multicollinearity, each WBC-based marker was included in the model separately. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Statistical analyses were primarily conducted using JMP software, version 17.0.0 (SAS Institute, Cary, NC, USA). In addition, restricted cubic spline analyses using the Cox proportional hazards model were performed in R software, version 4.5.1, with the survival and rms packages. P-values $<0.05$ were considered significant.

## III. Results

The mean age of the study participants was 62.9 ± 6.4 years, and 35.4% were men. During a mean follow-up duration of 13.5 years, 550 deaths were observed. Supplementary Figure 1 illustrates cubic splines showing the association between baseline WBC-based markers or serum inflammatory markers and the HRs for all-cause mortality. The baseline clinical characteristics of the study participants are summarized in **Table 1** separately for cases of death and survival. The death group was older, included more men and smokers, and had a higher prevalence of cancer and cardiovascular disease at baseline. hsCRP, AAT, NLR and SII were significantly higher, and LMR was significantly lower in the death group. Clinical characteristics of study populations in studies that investigated the prognostic significance of WBC-based markers are summarized in Supplementary Table 1. Our study population had a relatively small body size, a low frequency of smokers and patients with diabetes, and a low mortality rate. In addition, levels of WBC-based markers in this population were better than those in other populations.

**Table 2** shows mortality rates by the quintiles of each inflammatory marker. Differences in the survival curves among the quintiles (**Figure 1**) were statistically significant for all markers. Because the clinical characteristics differed significantly among the quintiles (Supplementary **Tables 2-7**), a covariate-adjusted Cox proportional hazards model analysis was performed to identify markers independently associated with all-cause mortality (**Table 3**). AAT showed marked association with mortality even when individuals with circulating AAT levels less than 100 mg/dL (n = 130), possible cases of congenital AAT deficiency, were excluded from the analysis (Supplementary **Table 8**). Other markers, namely PLR, SII, LMR, and hsCRP, but not NLR, were also associated with mortality, although the significance was relatively weak. When the conventional inflammatory markers and one of the significant WBC-based inflammatory markers were included in the same model, PLR and SII were independently associated with all-cause mortality along with AAT (PLR [Q5] HR = 1.38, 95% CI: 1.13–1.69, P = 0.002, SII [Q5] HR = 1.27, 95% CI: 1.05–1.54. P = 0.014) (**Table 4**). hsCRP did not show significant association in any model. **Figure 2** shows crude HR for all-cause mortality by the combination of AAT and PLR or SII, indicating a stepwise association between the combined markers and all-cause mortality. For the combination of PLR and AAT, the highest HR was observed in the group with both high PLR and high AAT (HR = 2.74, 95% CI: 2.05–3.67, P < 0.001), followed by the group with high AAT only (HR = 2.20, 95% CI: 1.80–2.69, P < 0.001), and the group with high PLR only (HR = 1.17, 95% CI: 0.91–1.50, P = 0.232), using the group with neither high PLR nor high AAT as the reference. Similarly, for the combination of SII and AAT, the highest HR was observed in the group with both high SII and high AAT (HR = 2.89, 95% CI: 2.23–3.76, P < 0.001), followed by the group with high AAT only (HR = 2.23, 95% CI: 1.81–2.76, P < 0.001), and the group with high SII only (HR = 1.46, 95% CI: 1.14–1.87, P = 0.003), using the group with neither high SII nor high AAT as the reference.

Supplementary **Figure 2** shows changes in the adjusted HR of each marker with increasing follow-up duration. The HR of AAT was consistently significant, whereas those of other markers decreased gradually, indicating that the prognostic significance of each marker varied with follow-up duration.

## IV. Discussion

In this longitudinal study of a large general population, we showed that conventional inflammatory markers (such as AAT) and WBC-based markers (such as PLR and SII) were independently associated with all-cause mortality. The HRs increased linearly with the combination of these

**Table 2** Summary statistics of mortality rate by inflammatory marker quintile

| | Quintiles | | | | |
|---|---|---|---|---|---|
| ***NLR*** | Q1 | Q2 | Q3 | Q4 | Q5 |
| Person-years | 16,194 | 16,155 | 16,108 | 16,140 | 15,988 |
| All-cause mortality | 84 | 104 | 103 | 107 | 152 |
| Mortality rate | 51.9 | 64.4 | 63.9 | 66.3 | 95.1 |
| ***PLR*** | | | | | |
| Person-years | 15,982 | 16,176 | 16,241 | 16,188 | 16,011 |
| All-cause mortality | 134 | 103 | 95 | 88 | 130 |
| Mortality rate | 83.8 | 63.7 | 58.5 | 54.4 | 81.2 |
| ***SII*** | | | | | |
| Person-years | 16,098 | 16,210 | 16,210 | 16,121 | 15,958 |
| All-cause mortality | 107 | 97 | 92 | 101 | 153 |
| Mortality rate | 66.5 | 59.8 | 56.8 | 62.7 | 95.9 |
| ***LMR*** | | | | | |
| Person-years | 15,902 | 16,165 | 16,067 | 16,246 | 16,216 |
| All-cause mortality | 169 | 121 | 110 | 88 | 62 |
| Mortality rate | 106.3 | 74.9 | 68.5 | 54.2 | 38.2 |
| ***hsCRP*** | | | | | |
| Person-years | 16,255 | 16,100 | 16,306 | 16,015 | 15,920 |
| All-cause mortality | 72 | 95 | 100 | 134 | 149 |
| Mortality rate | 44.3 | 59.0 | 61.3 | 83.7 | 93.6 |
| ***AAT*** | | | | | |
| Person-years | 15,199 | 16,276 | 15,533 | 17,661 | 15,929 |
| All-cause mortality | 72 | 77 | 87 | 118 | 196 |
| Mortality rate | 47.4 | 47.3 | 56.0 | 66.8 | 123.0 |

The mortality rate is shown per 10,000 person-years.
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; LMR, lymphocyte-to-monocyte ratio; hsCRP, high-sensitivity C-reactive protein; AAT, α1-antitrypsin.

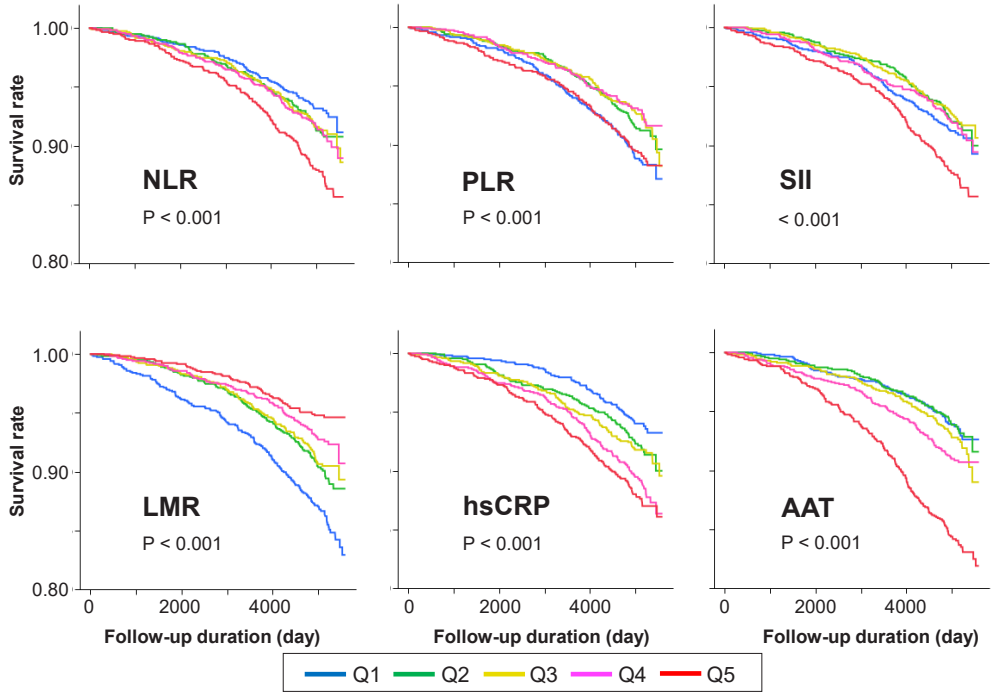


**Figure 1** Kaplan-Meier curve for all-cause mortality. Statistical significance was assessed by log-rank test. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, SII: systemic immune-inflammation index, LMR: lymphocyte-to-monocyte ratio; hsCRP, high-sensitivity C-reactive protein; AAT, α 1-antitrypsin.

**Table 3** Cox proportional hazards model analysis for all-cause mortality across quintiles of inflammatory markers (N = 5,970)

| | | HR (95% CI) | P |
|---|---|---|---|
| ***NLR*** | Q1 | Reference | |
| | Q2 | 1.06 (0.80–1.42) | 0.686 |
| | Q3 | 1.04 (0.78–1.39) | 0.782 |
| | Q4 | 1.01 (0.75–1.34) | 0.967 |
| | Q5 | 1.28 (0.97–1.67) | 0.078 |
| ***PLR*** | Q1 | Reference | |
| | Q2 | 0.92 (0.71–1.20) | 0.551 |
| | Q3 | 0.86 (0.66–1.13) | 0.284 |
| | Q4 | 0.86 (0.65–1.13) | 0.284 |
| | Q5 | 1.32 (1.03–1.70) | 0.031 |
| ***SII*** | Q1 | Reference | |
| | Q2 | 0.90 (0.69–1.19) | 0.478 |
| | Q3 | 0.87 (0.66–1.15) | 0.324 |
| | Q4 | 0.95 (0.72–1.25) | 0.716 |
| | Q5 | 1.29 (1.00–1.65) | 0.049 |
| ***LMR*** | Q1 | 1.39 (1.02–1.90) | 0.035 |
| | Q2 | 1.18 (0.86–1.62) | 0.296 |
| | Q3 | 1.27 (0.93–1.75) | 0.134 |
| | Q4 | 1.20 (0.86–1.66) | 0.284 |
| | Q5 | Reference | |
| ***hsCRP*** | Q1 | Reference | |
| | Q2 | 1.22 (0.89–1.66) | 0.210 |
| | Q3 | 1.19 (0.87–1.62) | 0.285 |
| | Q4 | 1.49 (1.10–2.01) | 0.001 |
| | Q5 | 1.33 (0.98–1.80) | 0.068 |
| ***AAT*** | Q1 | Reference | |
| | Q2 | 0.94 (0.68–1.30) | 0.710 |
| | Q3 | 1.09 (0.79–1.49) | 0.602 |
| | Q4 | 1.08 (0.80–1.46) | 0.599 |
| | Q5 | 1.73 (1.31–2.29) | < 0.001 |

Adjusted standard factors were age, sex, body mass index, current smoking, heavy drinking, history of cancer, history of cardiovascular disease, mean blood pressure, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, albumin, alanine aminotransferase, and gamma-glutamyl transferase.
HR; hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index, LMR, lymphocyte-to-monocyte ratio; hsCRP, high-sensitivity C-reactive protein; AAT, α1-antitrypsin.

**Table 4** Cox proportional hazards model analysis of all-cause mortality (N = 5,970)

| | | HR (95% CI) | P |
|---|---|---|---|
| Model 1 | PLR (Q5) | 1.38 (1.13–1.69) | 0.002 |
| | hsCRP (Q4 or Q5) | 1.09 (0.90–1.31) | 0.388 |
| | AAT (Q5) | 1.61 (1.34–1.94) | <0.001 |
| Model 2 | SII (Q5) | 1.27 (1.05–1.54) | 0.014 |
| | hsCRP (Q4 or Q5) | 1.08 (0.89–1.30) | 0.440 |
| | AAT (Q5) | 1.59 (1.32–1.92) | <0.001 |
| Model 3 | LMR (Q1) | 1.23 (0.93–1.36) | 0.230 |
| | hsCRP (Q4 or Q5) | 1.09 (0.91–1.32) | 0.339 |
| | AAT (Q5) | 1.63 (1.35–1.96) | <0.001 |

Adjusted factors were age, sex, body mass index, current smoking, heavy drinking, history of cancer, history of cardiovascular disease, mean blood pressure, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, albumin, alanine aminotransferase, gamma-glutamyl transferase and AAT.
HR; hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune–inflammation index; hsCRP, high-sensitivity C-reactive protein; AAT, α 1-antitrypsin.

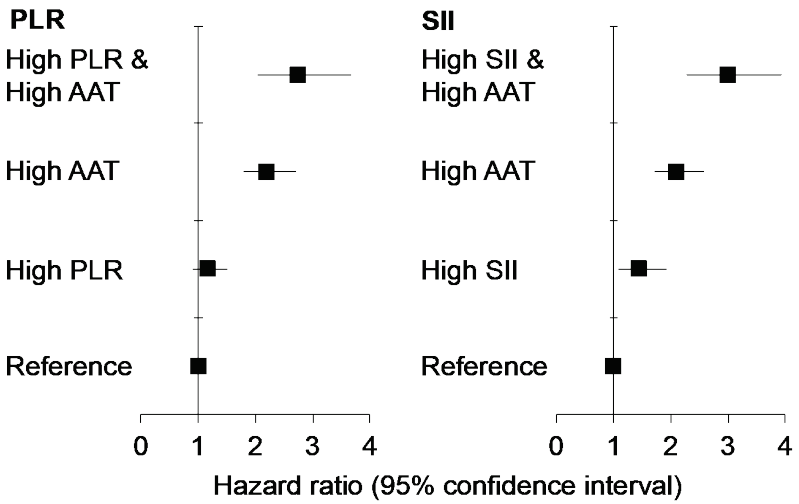


**Figure 2** Crude hazard ratio for all-cause mortality.
High α 1-antitrypsin (AAT): ≥ 146 mg/dL; high platelet-to-lymphocyte ratio (PLR): ≥ 144; high systemic immune-inflammation index (SII): ≥ 495.

markers.

PLR and SII were significantly associated with all-cause mortality. However, their HRs in the combination analysis with AAT were substantially smaller than that of AAT, which did not support PLR and SII use in population health practice, despite their ease of measurement. The lack of or weak associations was possibly due to our study population being relatively healthy, with low BMI, less frequent smoking and diabetes, and low mortality rates, compared with previous studies that reported the prognostic significance of WBC-based markers. In addition, NLR, PLR, and SII levels were lower in our study population. Although it is difficult to directly compare the results of our study with those of previous studies owing to large population differences including ethnicity, WBC-based markers may be useful in populations with more pronounced systemic inflammations.

In our previous analysis of the Nagahama study population, we found that AAT and hsCRP were independently associated with all-cause mortality [8]. However, in the current analysis of the same population with approximately 4 years of extended follow-up period, the HRs of hsCRP did not reach statistical significance when hsCRP and AAT were included in the same model. A reason for the discrepancy may lie in the gradual decreases in the HR of hsCRP in proportion to follow-up duration. The HRs of PLR, SII, and LMR also showed gradual decline, and a similar trend was observed in the analysis of NLR in the Rotterdam study [24] and the National Health and Nutrition Examination Survey [25], indicating that hsCRP and WBC-based markers may be useful in predicting relatively short-term prognosis. In contrast, AAT was associated with all-cause mortality in a study with a follow-up of more than 10 years probably due to AAT indicating long-term persistent low-level inflammation [31].

Several studies on the prognostic significance of WBC-based markers did not include CRP in the model, in order to examine the usefulness of WBC-based markers as a proxy for CRP [15,22,23,25,27-29]. In our study, WBC-based markers did not show clear associations with mortality even when hsCRP and AAT were not included in the model, indicating a limited usability of WBC-based markers. In settings where it is easily measurable, such as Japan, CRP is preferred for the assessment of potential inflammation in a general population. Our results strongly suggest that AAT should also be emphasized as an inflammatory marker in addition to CRP.

A strength of this study was the large sample size and availability of various clinical measures, which allowed for a comparison of the prognostic significance of WBC-based and conventional inflammatory markers. However, several study limitations should be considered with caution in interpreting the results. First, we did not consider cause of death owing to the limited number of deaths. Given the results of previous studies, WBC-based markers may be closely associated with cancer and cardiovascular mortalities. Second, WBC differential counts were measured using an automated hematology analyzer, whereas the visual method is considered as an objective standard. However, any discrepancies in the counts due to the differences in measurement methods were small. The use of automated hematology analyzers may not significantly affect the present results.

In conclusion, AAT was identified as a good marker for long-term mortality risk assessment in the general population. Some of WBC-based inflammatory markers were

associated with mortality, although the prognostic significance was limited when WBC-based inflammatory markers were considered individually. However, combining these markers with AAT might be useful for identifying populations at higher risk.

**Author Contributions**

**AS:** Conceptualization, Methodology, Formal analysis, Writing - Original Draft. **KS:** Supervision, Investigation, Data Curation. **TK:** Supervision, Investigation, Data Curation. **TN:** Supervision, Project administration, Funding acquisition. **FM:** Supervision, Project administration, Funding acquisition. **YT:** Conceptualization, Methodology, Investigation, Resources, Data Curation, Supervision, Project administration, Funding acquisition, Writing – review & editing.

**Acknowledgements**

We would like to thank all members of the Nagahama study group for their assistance in conducting the Nagahama study. We are very grateful to the Nagahama City Office and the non-profit organization, Zeroji Club, for their assistance in the Nagahama study. We would like to thank Editage (www.editage.jp) for English language editing.

**Conflict of Interest**

The authors have no conflicts of interest directly relevant to the content of this article.

**Financial Support**

The work was supported by a university grant, the Center of Innovation Program, the Global University Project from the Ministry of Education, Culture, Sports, Science and Technology of Japan (25293141, 26670313, 25253059, 26293198, 17H04182, 17H04126, 18K18450, 17H04123, 21H04850); the Practical Research Project for Rare/Intractable Diseases (ek0109070, ek0109283, ek0109196, ek0109348), the Program for an Integrated Database of Clinical and Genomic Information (kk0205008), the Research and Development Grants for Dementia (dk0207006, dk0207027), the Practical Research Project for Lifestyle-related Diseases including Cardiovascular Diseases and Diabetes Mellitus (ek0210066, ek0210096, ek0210116), the Research Program for Health Behavior Modification by Utilizing IoT (le0110005, le0110013), the Research and Development Grants for Longevity Science (dk0110040) from the Japan Agency for Medical Research and Development (AMED), Takeda Medical Research Foundation, Mitsubishi Foundation, Daiwa Securities Health Foundation, and Sumitomo Foundation.

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