The Platelet Count Can Predict In-hospital Death in HIV-negative Smear-positive Pulmonary Tuberculosis Inpatients

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Abstract:
Objective This retrospective cohort study investigated whether the three components of the blood cell count have prognostic implications in HIV-negative Japanese adult inpatients with smear-positive pulmonary tuberculosis.
Methods We reviewed patients who were treated by the isoniazid, rifampicin, pyrazinamide, and ethambutol regimen or by the isoniazid, rifampicin, and ethambutol regimen. The association between the patient data on admission and the survival outcome was evaluated.
Results We reviewed 367 consecutive patients (male, 60.5%) with a median age of 72 [interquartile range (IQR), 54-82] years. While the white blood cell count did not differ between the two groups, (discharged alive: 7,000/μL; IQR, 5,500-9,300; died in hospital: 7,200/μL; IQR, 5,600-9,400; p=0.797), hemoglobin level (discharged alive: 11.5 g/dL; IQR, 10.0-13.1; died in hospital: 9.9 g/dL; IQR, 8.6-11.3; p<0.001) and the platelet count (discharged alive: 275,000/μL; IQR, 206,000-345,000; died in hospital: 149,000/μL; IQR, 93,000-236,000; p<0.001) were lower in patients who died in hospital. After dividing patients into hemoglobin- and platelet-based quantiles, the lower quantile class tended to show poorer survival (log-rank test for trend p<0.001 for both). A multi-variable Cox proportional hazards model revealed that hazard ratio for in-hospital death for every 1,000/μL increase of platelet count was 0.997 (95%CI, 0.995-0.999; p=0.010); the hazard ratio for the hemoglobin level was not significant.
Conclusion A low platelet count was clearly related to a poor life prognosis in HIV-negative Japanese adult inpatients with smear-positive pulmonary tuberculosis.

Key words: blood cell count, cohort studies, anti-bacterial agents, blood platelets, pulmonary tuberculosis

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Introduction

Although the incidence of pulmonary tuberculosis (TB) has fallen by an average of 1.5% per year since 2000, this prevalent infectious disease, which is caused by Mycobacterium tuberculosis, remains a considerable public health problem in this century. In 2015, 10.4 million people were newly infected with tuberculosis, and 1.8 million people died from this disease every year (1). TB is highly prevalent in Asian, Pacific, and African developing countries, including India, Indonesia, China, Nigeria, Pakistan, and South Africa (1). People in these countries often face conditions such as poverty, starvation, high-HIV prevalence, poor mental health, and the lack of a proper medical system. Known risk factors for the acquisition of TB infection include a low socio-economic status, HIV infection, diabetes, immunosuppression, old age, and malnutrition (2-4). Currently, the ma-

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majority of TB patients can be saved once an appropriate antibiotic regimen is administered after a proper diagnosis. Nonetheless, a certain proportion of patients with pulmonary TB die. Some risk factors for death from TB have already been revealed, these include old age, dehydration, respiratory failure, decreased activity of daily living, and malnutrition (5-7). However, much still remains to be clarified. Blood cell counts have been widely analyzed in the clinical setting since the automated counter was developed in the 1950s and 1960s (8). Since then, the blood cell count has become an essential blood test. Although the blood cell count has different meanings depending on the clinical background, leukocytosis most commonly implies elevated inflammation due to bacterial infection, while a decreased hemoglobin level suggests iron deficiency and chronic inflammation, and a low platelet count indicates a high risk of bleeding (9, 10). In addition, recent studies have revealed that—in addition to white blood cells—platelets are involved in the defense mechanism (11, 12). Thus, a low platelet count might indicate the lack of a proper immune system. We wondered if the blood cell count at the time of admission due to pulmonary TB predicts the risk of death. The aim of the current retrospective cohort study was to investigate whether the three major components of the blood cell count have prognostic implications for HIV-negative Japanese inpatients with smear-positive pulmonary TB.

Materials and Methods

This retrospective chart review study followed the Ethical Guidelines for Medical and Health Research Involving Human Subjects published in 2015 by the Ministry of Health, Labor and Welfare, Japan (13). The requirement of informed consent was waived because this study had a retrospective observational design. The Institutional Review Board of Yokohama City University approved the study protocol.

Inclusion criteria

We retrospectively obtained data on patients who satisfied the following criteria: (i) hospitalized with smear-positive pulmonary tuberculosis; (ii) HIV-negative; (iii) admitted to an isolation ward of our hospital between January 2007 and October 2015; (iv) ≥16 years of age; and (v) anti-TB antibiotic treatment was initiated on admission. The following patients were excluded from the study: (i) patients who had already started treatment for the current infection in another hospital (transferred-in cases); (ii) patients who were discharged alive before negative infectivity was confirmed (transferred-out cases); and (iii) patients with multi-drug resistant infection. If a patient was admitted more than once, only the data from the first admission was used.

The diagnosis of TB required one or more polymerase chain reactions, and a loop-mediated isothermal amplification assay, or culture (4). The HIV status of every patient was routinely checked on admission.

Antibiotic regimens

After admission, directly observed treatment was started. Our preferred regimen is the combination of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for two months followed by isoniazid and rifampicin for four months (2, 14). The alternative regimen is the combination of isoniazid, rifampicin, and ethambutol (HRE) for two months followed by isoniazid and rifampicin for seven months (2, 14). Physicians mainly selected the alternative HRE regimen for patients who were deemed to be at high risk for drug-induced liver injury due to factors such as old age or liver disease. When neither HRZE nor HRE was appropriate, other regimens were considered. The dosage of each medication was as follows: isoniazid (5 mg/kg/day; maximum 300 mg/day), rifampicin (10 mg/kg/day; maximum 600 mg/day), pyrazinamide (25 mg/kg/day; maximum 1,500 mg/day), and ethambutol (15-20 mg/kg/day; maximum 750-1,000 mg/day) (14).

Baseline assessments

The medical history including co-morbidities was judged based on history taking from the patients, their family, and a referral letter. A chest X-ray was routinely taken and evaluated by physicians independent of this study. Blood tests were carried out on the day of admission by an in-hospital laboratory that has been accredited by the International Organization for Standardization 15189 since 2010.

Outcomes

Patients were discharged when they satisfied all of the following criteria (15): (i) the patient was taking effective chemotherapy, (ii) clinical improvement was proven, (iii) non-infectiveness was confirmed based on three or more consecutive smear-negative or culture-negative sputum samples obtained on different days. Sputum specimens were taken once a week.

The cause of death was judged based on the patient’s death certificate.

Statistics

Continuous variables were presented as the median and interquartile range (IQR). A Mann-Whitney U test and Fisher’s exact test were used to compare non-parametric non-paired continuous variables and binary variables, respectively. A chi-squared test was used to assess a 2×3 table of treatment regimens. The Mann-Whitney U test was used to compare susceptibility in two groups. A log-rank test for trend was used to compare the survival curves. A multi-variable Cox proportional hazards model was used to estimate the hazard ratio (HR). Variables that had a p value of <0.05 in a univariate analysis were input for forward stepwise variable selection. A p value of 0.2 was the cutoff value for forward stepwise variable selection.

All of the analyses were performed using the GraphPad Prism software program (version 6.0, GraphPad Software,
San Diego, USA) and Excel Toukei 2012 (SSRI, Tokyo, Japan).

### Results

#### Background characteristics

We reviewed 367 consecutive patients who satisfied the inclusion criteria. This group consisted of 222 men (60.5%) and 145 women (39.5%) with a median age of 72 (IQR, 54-82) years.

Among the 367 patients in our cohort, 153 (41.7%) had one or more pulmonary cavities on X-ray. Bilateral infiltration on X-ray was observed in 270 (73.6%) patients (Table 1). The medians white blood cell count, hemoglobin level, and platelet count were 7,000/μL (IQR: 5,500-9,300), 11.1 g/dL (IQR: 9.7-12.6), and 252,000/μL (IQR: 172,000-335,000), respectively.

Forty-one patients (11.2%) had history of previous TB treatment. The pathogens from 0.5% and 1.1% of patients were resistant to isoniazid and rifampicin, respectively. These rates did not differ between non-survivors and survivors (p=0.586 for isoniazid, p=0.812 for rifampicin).

### Table 1. Background Patient Characteristics, Treat Regimen, and Outcomes.

|                  | All   | Discharged alive | Died in hospital | p    |
|------------------|-------|------------------|------------------|------|
| N                | 367   | 292              | 75               |      |
| Age (years)      | 72 (54-82) | 67 (48-79) | 83 (76-87) | <0.001 |
| Sex (female)     | 145 (39.5%) | 111 (38.0%) | 34 (45%) | 0.290  |
| Cavity on X-ray  | 153 (41.7%) | 124 (42.5%) | 29 (39%) | 0.601  |
| Bilateral infiltration on X-ray | 270 (73.6%) | 204 (69.9%) | 66 (88%) | 0.001  |
| Smear on admission ≥2 | 202 (55.0%) | 158 (54.1%) | 44 (59%) | 0.517  |
| Previous history of TB treatment | 41 (11.2%) | 32 (11.0%) | 9 (12%) | 0.837  |
| Concomitant extra-pulmonary TB | 38 (10.4%) | 31 (10.6%) | 7 (9%) | 0.835  |
| Diabetes         | 100 (27.2%) | 82 (28.1%) | 18 (24%) | 0.562  |
| Immunosuppressant use | 44 (12.0%) | 28 (9.6%) | 16 (21%) | 0.009  |
| Chronic cardiac disease | 53 (14.4%) | 34 (11.6%) | 19 (25%) | 0.005  |
| Chronic pulmonary disease | 43 (11.7%) | 31 (10.6%) | 12 (16%) | 0.226  |
| Chronic liver disease | 41 (11.2%) | 25 (8.6%) | 16 (21%) | 0.004  |
| Chronic renal disease | 43 (11.7%) | 29 (9.9%) | 14 (19%) | 0.044  |
| Active malignancy | 42 (11.4%) | 27 (9.3%) | 15 (20%) | 0.014  |
| White blood cell (/μL) | 7,000 (5,500-9,300) | 7,000 (5,500-9,300) | 7,200 (5,600-9,400) | 0.797  |
| Hemoglobin (g/dL) | 11.1 (9.7-12.6) | 11.5 (10.0-13.1) | 9.9 (8.6-11.3) | <0.001 |
| Platelet (1,000/μL) | 252 (172-335) | 275 (206-345) | 149 (93-236) | <0.001 |
| Total protein (g/dL) | 6.6 (5.9-7.2) | 6.8 (6.2-7.3) | 5.5 (5.0-6.2) | <0.001 |
| Albumin (g/dL) | 2.8 (2.2-3.6) | 3.1 (2.5-3.8) | 2.0 (1.7-2.3) | <0.001 |
| Aspartate aminotransferase (IU/dL) | 25 (19-43) | 24 (18-37) | 36 (26-70) | <0.001 |
| Alanine transaminase (IU/dL) | 18 (12-32) | 17 (12-30) | 20 (14-42) | 0.046  |
| Total bilirubin (mg/dL) | 0.6 (0.4-0.9) | 0.5 (0.4-0.8) | 0.8 (0.5-1.5) | <0.001 |
| Creatinine (mg/dL) | 0.65 (0.51-0.90) | 0.65 (0.53-0.87) | 0.63 (0.49-1.07) | 0.870  |
| C-reactive protein (mg/dL) | 3.80 (0.98-7.82) | 3.21 (0.64-6.59) | 7.75 (4.67-11.45) | <0.001 |

Susceptibility

|                  | All   | Discharged alive | Died in hospital | p    |
|------------------|-------|------------------|------------------|------|
| Isoniazid-susceptible | 333 (90.7%) | 265 (90.8%) | 68 (90.7%) | 0.586  |
| Isoniazid-intermediate | 6 (1.6%) | 5 (1.7%) | 1 (1.3%) |      |
| Isoniazid-resistant | 2 (0.5%) | 2 (0.7%) | 0 (0.0%) |      |
| Isoniazid-unclear | 26 (7.1%) | 20 (6.8%) | 6 (8.0%) |      |
| Rifampicin-susceptible | 343 (93.5%) | 274 (93.8%) | 69 (92.0%) | 0.812  |
| Rifampicin-intermediate | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |      |
| Rifampicin-resistant | 4 (1.1%) | 3 (1.0%) | 1 (1.3%) |      |
| Rifampicin-unclear | 20 (5.4%) | 15 (5.1%) | 5 (6.7%) |      |

Treatment regimen

|                  | All   | Discharged alive | Died in hospital | p    |
|------------------|-------|------------------|------------------|------|
| HRZE             | 213 (58.0%) | 195 (66.8%) | 18 (24.0%) | <0.001 |
| HRE              | 124 (33.8%) | 81 (27.7%) | 43 (57.3%) |      |
| Other regimen    | 30 (8.2%) | 16 (5.5%) | 14 (18.7%) |      |

p: comparison between patients who were discharged alive and those who died in hospital. Susceptibility data were only tested for S/I/R after excluding unclear.

(Brackets) indicate interquartile range for continuous variables or percentage for binary variables.

HRZE: isoniazid, rifampicin, pyrazinamide, and ethambutol, HRE: isoniazid, rifampicin, and ethambutol
Comparison of survivors and non-survivors

In our cohort, 292 (79.6%) patients were discharged alive and 75 (20.4%) patients died in hospital. The cause of death was tuberculosis for 62 patients. The other 13 patients died of other causes. There was one death each from the following: brain bleeding, brain infarction, myocardial infarction, heart failure, pneumonia, lung cancer, hepatic-cell carcinoma, liver cirrhosis, chronic hepatitis C infection, autoimmune hepatitis, panperitonitis, renal failure, and sepsis. Thus, major bleeding was the cause of death of one patient with pulmonary TB, whose platelet count on admission was 172,000/μL. The median duration of hospitalization of the patients who were discharged alive (survivors) was 67 (IQR 42–97) days, while that of the patients who died in hospital (non-survivors) was 26 (IQR 12–59) days.

In comparison to the patients who were discharged alive, the non-survivors were older [survivors, 67 years (IQR: 48–79), non-survivors 83 years (IQR: 76–87), p<0.001] and frequently had bilateral infiltration on X-ray (survivors, 69.9%; non-survivors, 88%; p=0.001), immunosuppressant usage (survivors, 9.6%, non-survivors, 21%; p=0.009), chronic cardiac disease (survivors, 11.6%, non-survivors, 25%; p=0.005), chronic liver disease (survivors, 8.6%, non-survivors, 21%; p=0.004), chronic renal disease (survivors, 9.9%, non-survivors, 19%; p=0.044), and active malignancy (survivors, 9.3%, non-survivors, 20%; p=0.014) (Table 1). The non-survivors also had higher aspartate aminotransferase [survivors, 24 IU/dL (IQR: 18–37); non-survivors, 36 IU/dL (IQR: 26–70); p<0.001], total bilirubin [survivors, 0.5 mg/dL (IQR: 0.4–0.8); non-survivors, 0.8 mg/dL (IQR: 0.5–1.5); p<0.001], and C-reactive protein [survivors, 3.21 mg/dL (IQR: 0.64–6.59); non-survivors, 7.75 mg/dL (IQR: 4.67–11.45); p<0.001] levels. The non-survivors had lower total protein [survivors, 6.8 g/dL (IQR: 6.2–7.3), non-survivors, 5.5 g/dL (IQR: 5.0–6.2); p<0.001] and serum albumin [survivors, 3.1 g/dL (IQR: 2.5–3.8); non-survivors, 2.0 (IQR: 1.7–2.3); p<0.001] levels (Table 1).

Blood cell counts and in-hospital death

Although the white blood cell count did not differ between the two groups, [survivors, 7,000/μL (IQR: 5,500–9,300); non-survivors, 7,200/μL (IQR: 5,600–9,400); p=0.797], the non-survivors showed lower hemoglobin levels [survivors, 11.5 g/dL (IQR: 10.0–13.1); non-survivors, 9.9 g/dL (IQR: 8.6–11.3); p<0.001] and platelet counts [survivors, 275,000/μL (IQR: 206,000–345,000); non-survivors, 149,000/μL (IQR: 93,000–236,000); p<0.001] (Table 1 and Fig. 1).

The receiver operating characteristic curves for in-hospital death according to the blood counts are shown in Fig. 2. The areas under the curve for the white blood cell count, hemoglobin level, and platelet count were 0.51 0.72, and 0.75, respectively (Fig. 2).
After dividing the patients into hemoglobin- and platelet-based quantiles, the lower quantile class tended to show poorer survival (log-rank test for trend \( p<0.001 \) for both) (Fig. 3). However, the survival curves of four white blood cell quartiles frequently overlapped with each other (\( p=0.892 \)).

**The Cox proportional hazards model**

Among the variables that showed significant differences in the univariate analysis (Table 1), eight were selected by the forward stepwise method for the multi-variable Cox proportional model for in-hospital death. The HR for in-hospital death for every 1,000/μL increase of platelet count was 0.997 (95%CI 0.995-0.999, \( p=0.010 \)). This was equivalent to an HR of 0.73 (95%CI 0.58-0.93) for every 100,000/μL increase of platelet count.

In addition to the platelet count, age [HR 1.07 (95%CI 1.04-1.10); \( p<0.001 \)], active malignancy [HR 1.97 (95%CI 1.08-3.60); \( p=0.027 \)], the albumin level [HR 0.97 (95%CI 0.995-0.999); \( p=0.010 \)], the aspartate aminotransferase level [HR 1.003 (95%CI 1.001-1.005); \( p=0.003 \)], and the total bilirubin level [HR 1.18 (95%CI 1.05-1.33); \( p=0.005 \)] were found to be significant predictors of in-hospital death.

The hemoglobin level was excluded from this model, which suggested that hemoglobin was not independently related to in-hospital death.

**Sensitivity and additional analyses**

We conducted a sensitivity analysis in which patients who died from non-TB causes were excluded. The area under the curve for the platelet count was 0.73. The Mann-Whitney \( p \) value was <0.001. A Cox model that included the variables shown in Table 2 suggested that a low platelet count was also related to a high risk of death in this cohort (HR 0.997; 95%CI 0.994-0.9997; \( p=0.028 \)).

The Kaplan-Meier curve showed that patients with a low-platelet count on admission had high mortality during the first month of hospitalization. Among 28 patients with the lowest platelet count quartiles, who died in the first 28 days, the rates of chronic heart disease (30%) and chronic liver disease (30%) were remarkably high. Only five patients were treated by a four-drug regimen. The HRE regimen and non-standard regimen were used for fifteen and seven patients, respectively.

**Discussion**

To the best our knowledge, this is the first study to evaluate whether the three components of the blood cell count have prognostic implications in HIV-negative Japanese inpatients with smear-positive pulmonary TB. Among the three components, the platelet count was the only marker that predicted in-hospital death. We believe that the association be-

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**Figure 3.** Kaplan-Meier survival curves. Bold solid line: The first (lowest) quantile. Bold broken line: The second quantile. Thin solid line: The third quantile. Thin broken line: The fourth (highest) quantile. Patients discharged alive were censored.

**Table 2.** Cox Proportional Hazards Model for Death.

| Hazard ratio (95%CI) | \( p \) |
|----------------------|--------|
| Age (year)           | 1.07 (1.04-1.10) | <0.001 |
| Active malignancy    | 1.97 (1.08-3.60) | 0.027 |
| Platelet (1,000/μL)  | 0.997 (0.995-0.999) | 0.010 |
| Albumin (g/dL)       | 0.27 (0.16-0.46)  | <0.001 |
| Aspartate aminotransferase (IU/dL) | 1.003 (1.001-1.005) | 0.003 |
| Total bilirubin (mg/dL) | 1.18 (1.05-1.33) | 0.005 |
| C-reactive protein (mg/dL) | 1.04 (0.99-1.09) | 0.089 |
| Treated by non-standard regimen | 1.67 (0.86-3.25) | 0.130 |

Non-standard regimen: regimens other than HRZE and HRE.
between the platelet count and mortality is plausible for various reasons. First, our database was reliably large. Second, numerous analyses have consistently indicated that a low platelet count at admission was related to death. Third, there may be biologically persuasive explanations for the link between a decreased platelet count and TB death.

Our observational study cannot directly answer why a low platelet count is associated with a high risk of death. One possibility is that a decreased platelet count indicates a decreased liver function. The platelet count may be a confounding factor between the liver function and TB death. The liver is a vital organ for nutrition storage, albumin synthesis, and drug metabolism. Actually, in the analysis of this study, some liver-related laboratory tests (i.e., total bilirubin, albumin, and aspartate aminotransferase) were included in the final Cox model. Among these factors, a low albumin level was found to be a key risk factor of TB death (Table 2) (5, 6). Thus, our primary hypothesis is that a decreased platelet count is a surrogate marker for the liver function and nutrition.

Another credible explanation for the link between the low platelet count and a high risk of death is that the platelet count was used as a marker of the defense mechanism to TB bacilli in the lung (11, 12). Direct phagocytosis of invading particles and bacilli is one of the defense mechanisms by platelets (11). In addition, platelets activate cytotoxic T lymphocytes (16). Platelets also release antibacterial protein, thrombocidins, which are lethal to a range of bacteria (16). Furthermore, platelets activate the immune system of the lungs via numerous cytokines. In vivo studies have revealed that the platelet count (17) and platelet factor-4 level (12) are elevated in TB patients, especially in cases with extensive pulmonary infiltration. A decreased platelet count may indicate a decreased defense against co-morbid infection (18).

A low platelet count usually suggests a risk of bleeding. Thus, platelet transfusion was indicated for a patient with platelet count of <20,000/μL. However, the patients in our cohort did not die of major bleeding due to a low platelet count. In all of the fatal cases, the patients had a platelet count over 20,000/μL at admission (Fig. 1). Furthermore, one patient who died from major bleeding had a platelet count of 172,000/μL at admission. Thus, we do not think that bleeding caused by low platelet count was the main reason for in-hospital death.

Anemia was related to the risk of in-hospital death in a univariate analysis (Table 1 and Fig. 1-3). However, the hemoglobin level was eliminated from the multi-variable model (Table 2). The hemoglobin level of TB cases might simply be a surrogate of age and the nutritional status.

The present study was associated with some limitations. First, it was retrospective in nature, which might have induced bias. However, we believe that this simple study using a hard endpoint was not strongly biased by the study design. Second, our TB cohort mainly consisted of elderly individuals that reflected the East Asian epidemiology (Table 1). Thus, the findings should be validated in other cohorts, especially cohorts with younger patients, in the future. Third, our data showed that a low platelet count was related to TB death. However, the true causative factor of death among the patients with low-platelet counts was unclear.

Conclusion

In conclusion, we conducted a single-center retrospective study to evaluate the impact of the blood cell count on in-hospital death among HIV-negative Japanese inpatients with smear-positive pulmonary tuberculosis. Eventually, our results showed that a low platelet count was clearly related to a poor life prognosis in the patients of the present study.

The authors state that they have no Conflict of Interest (COI).

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