Observational Study

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Analysis of risk factors for pulmonary tuberculosis with persistent severe inflammation

An observational study

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Abstract

Introduction: Patients with pulmonary tuberculosis (TB) sometimes show persistent severe inflammation for more than 1 month, even if TB treatment is effective. Although this inflammation can be improved through continuous antituberculous therapy, the risk factors for persistent inflammation remain unclear. Therefore, we sought to study the characteristics of patients with persistent severe inflammation.

Materials and methods: We retrospectively analyzed 147 hospitalized adult patients with C-reactive protein (CRP) levels of 5 mg/dL or more on admission to Fukujuji Hospital from April 2019 to March 2021. The patients were divided into 2 groups: 40 patients (27.2%) had CRP levels of 5 mg/dL or more at 4 weeks after admission (persistent inflammation group), and 107 patients (72.8%) had CRP levels that fell below 5 mg/dL within 4 weeks of admission (improved inflammation group).

Results: The median CRP level on admission in the persistent inflammation group was 10.8 mg/dL (interquartile range 9.1–14.5), which was higher than that in the improved inflammation group (median 8.2 mg/dL [6.5–12.1], $P = .002$). Patients in the persistent inflammation group had a higher prevalence of large cavities, defined as cavities ≥4 cm in diameter, on chest computed tomography (CT) (n = 20 [50.0%] vs n = 12 [11.2%], $P < .001$).

Discussion and conclusions: This study showed that 27.2% of patients who had high or moderate inflammation on admission did not achieve low CRP levels within 4 weeks after admission. Risk factors for persistent severe inflammation in patients with TB were presence of a large cavity (cavity diameter ≥4 cm) on chest CT and a high CRP level on admission. Therefore, in a patient with a large cavity on chest CT and/or CRP ≥9.0 mg/dL on admission, long-term inflammation may occur despite antituberculous therapy if other diseases are ruled out.

Abbreviations: CRP = C-reactive protein, CT = computed tomography, IQR = interquartile range, TB = tuberculosis, WBC = white blood cell.

Keywords: c-reactive protein, persistent inflammation, severe cavitation, tuberculosis

1. Introduction

Pulmonary tuberculosis (TB) is a slowly progressive disease caused by *Mycobacterium tuberculosis*[1] and is associated with lower levels of inflammatory markers, such as C-reactive protein (CRP), than community-acquired pneumonia.[2] Previous studies have demonstrated that CRP levels in patients with TB are slightly (1–4.9 mg/dL) or moderately (5–10 mg/dL) increased.[3–6] In many patients with TB, CRP levels decrease rapidly for 1 to 2 weeks after the initiation of antituberculous therapy[7]; in some patients, however, CRP levels do not return to normal values for 2 months.[3,4] Furthermore, severe inflammation sometimes persists for more than 1 month, even if

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The study was approved by the Institutional Review Board of Fukujuji Hospital (study number: 21020). It was determined that patient consent was not needed. The decisions made by this board are based on and in accordance with the Declaration of Helsinki.

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The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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antituberculous therapy is effective[4]. Generally, inflammation improves slowly with continuous antituberculous therapy.[4] However, it is difficult to rule out inflammation due to other diseases, and the risk factors for persistent inflammation are unclear. Therefore, this study enrolled TB patients with CRP levels of 5 mg/dL or higher, representing a moderate to large increase from the normal level,[3] and investigated the characteristics of patients with persistent severe inflammation.

2. Materials and methods

2.1. Study design and setting

We retrospectively collected the data of 411 adult patients (age ≥18 years old) with pulmonary TB who were hospitalized at Fukujuji Hospital from April 2019 to March 2021. The flowchart of the study is shown in Figure 1. A total of 248 patients who showed low CRP levels (less than 5 mg/dL) on admission and 14 patients whose CRP levels could not be evaluated at 4 weeks after admission were excluded. The patients were divided into the persistent inflammation group and the improved inflammation group based on CRP levels at 4 weeks after admission. The data of 40 patients (27.2%) with moderate to high CRP levels (5 mg/dL or more) at 4 weeks after admission (the persistent inflammation group) and 107 patients (72.8%) who achieved low CRP levels (less than 5 mg/dL) within 4 weeks of admission (the improved inflammation group) were reviewed. Patients who did not show a decline in the CRP level to less than 5 mg/dL within 8 weeks were also evaluated. Data regarding symptoms, laboratory test results, radiological findings, and other relevant findings were collected. The study was approved by the Institutional Review Board of Fukujuji Hospital, and the requirement for patient consent was waived. The decisions made by the board were based on and in accordance with the Declaration of Helsinki (study number: 21020).

2.2. Definitions

In this study, the serum CRP level was considered an inflammatory parameter, as it is considered an early systemic marker of focal inflammation.[8] CRP levels were divided into 2 groups: a low CRP level was defined as less than 5 mg/dL, and a moderate to high CRP level was defined as 5 mg/dL or more.[3] The definition of persistent inflammation was based on a moderate to high CRP levels observed for more than 4 weeks after admission, and the definition of improved inflammation was based on a decrease in the CRP level to a low level within 4 weeks of admission. A decrease to less than 5 mg/dL was considered valid if a patient maintained a CRP level in this range for 7 days or more (although the first day of improved CRP was defined as the first day with a level of less than 5 mg/dL). Immunosuppressed status was considered when patients had malignancy, diabetes mellitus, use of steroids and/or immunosuppressant therapy before admission, and acquired immunodeficiency syndrome. The recommended antituberculous therapy regimens were isoniazid + rifampin + ethambutol ± pyrazinamide.[9] Drug-resistant TB was defined as TB that was resistant to isoniazid, rifampin, ethambutol, and/or pyrazinamide according to drug susceptibility testing with mycobacterial growth indicator tubes.

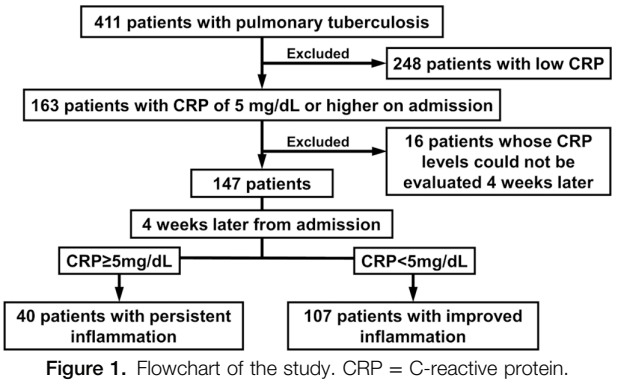

Figure 1. Flowchart of the study. CRP = C-reactive protein.

2.3. Classification of radiographic and computer tomographic findings

Using the classification of pulmonary TB designated by the Japanese Society for Tuberculosis, we evaluated TB cases based on the location, properties, and spread of lesions on radiography.[10] Lesion locations were classified as right, left, or bilateral.[10] Lesion spread was classified as follows:

1. the total area of the lesions did not exceed the area above the second rib,
2. the area of the lesions was between those of groups 1 and 3, and
3. the total area of the lesions exceeded the area of the unilateral lung field.[10]

Lesions were classified as type I, type II, or type III based on their properties: type I) the area of the cavity exceeded the area of group 1 lesions, and the total area of the lesions exceeded the area of the unilateral lung field; type II: the area of the cavity did not exceed the area of group 1 lesions; and type III: no cavities were present.[10] Computed tomography findings were classified as cavity, consolidation, miliary pattern, large cavity, cheese-like appearance, or pleural effusion (Fig. 2A-F). A large cavity was defined as an advanced lesion with a diameter of 4 cm or more (Fig. 2D),[11] and a cheese-like appearance was identified based on lobar consolidation with multiple small voids inside (Fig. 2E).[11]

2.4. Statistical methods

All data were analyzed and processed using EZR, version 1.53.[12] Student *t* test, the Mann–Whitney *U* test, Fisher's exact test, and binomial logistic regression analysis were used for group comparisons. The Kruskal–Wallis test was used to compare the location of lesions on radiography, and the Cochran–Armitage trend test was used to compare the properties and spread of lesions on radiography and an acid-fast bacillus smear of sputum. Bonferroni correction was used for pairwise comparisons for data with significant differences on the Kruskal–Wallis test and the Cochran–Armitage trend test. Sensitivities, specificities, and odds ratios were calculated. A receiver operating characteristic (ROC) curve was constructed and used to determine the cutoff values. The level of statistical significance was set at $P = .05$ (2-tailed).

3. Results

The baseline characteristics of the study subjects are shown in Table 1. The median age of the patients was not significantly

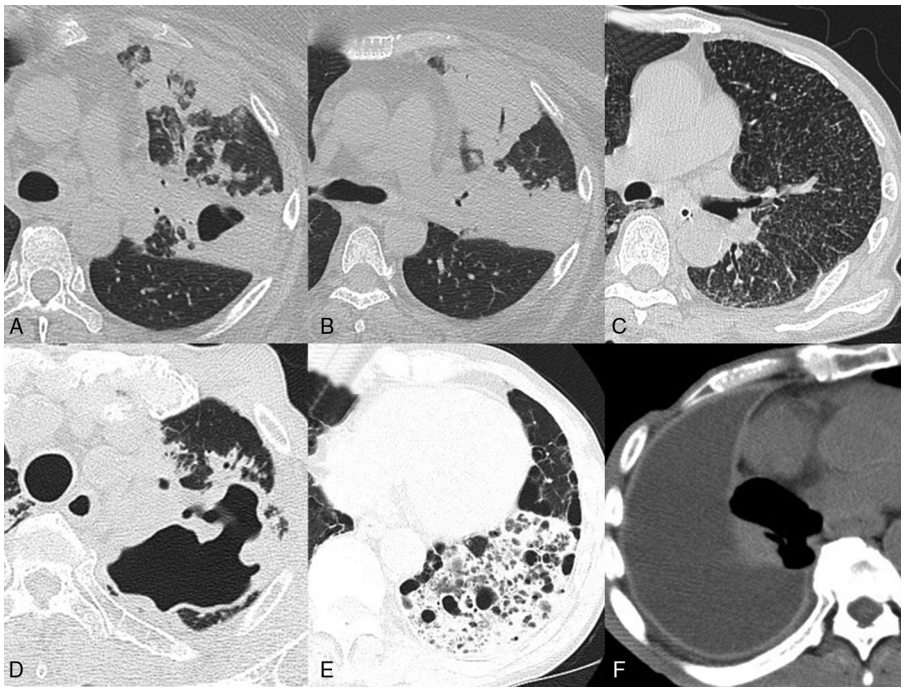

Figure 2. Classifications of CT findings. A: cavity; B: consolidation; C: miliary pattern; D: large cavity; E: cheese-like appearance; F: pleural effusion.

different between the persistent inflammation group and the improved inflammation group (median (interquartile range [IQR]) 67 years [58–79] vs 77 years [IQR: 56–88], $P = .110$), and the proportion of males in the persistent inflammation group was not significant difference to that in the improved inflammation group (n = 32 [80.0%] vs n = 74 [69.2%], $P = .220$). The results of acid-fast bacillus smears of sputum were not significantly different between the 2 groups (Cochran–Armitage trend test $P = .367$). According to the laboratory data, the patients in the persistent inflammation group had higher white blood cell (WBC) counts (median [IQR] 9930 cells/μL [7398–11,412] vs 7730 cells/μL [6065–9900], $P = .016$) and CRP levels (median [IQR] 10.8 mg/dL [9.1–14.5] vs 8.2 mg/dL [6.5–12.1], $P = .002$). Regarding the classification of pulmonary TB based on radiography, the location (Kruskal–Wallis test $P = .203$) and spread of lesions (Cochran–Armitage trend test $P = .232$) were not significantly different between the 2 groups. The properties of lesions showed a significant difference according to the Cochran–Armitage trend test ($P = .015$); however, each variable was not significantly different after Bonferroni correction (I vs II $P = .351$, I vs III $P = 0.99$, II vs III $P = .264$). The number of patients with large cavities was larger in the persistent inflammation group (n = 20 [50.0%] vs n = 12 [11.2%], $P < .001$). In the persistent inflammation group, side effects of antituberculous therapy (n = 20 [50.0%] vs n = 30 [28.0%], $P = .018$) and drug-resistant tuberculosis infection (n = 5 [12.5%] vs. n = 2 [2.8%], $P = .033$) occurred significantly more frequently. The side effects of antituberculous therapy included liver dysfunction (persistent inflammation group n = 7 [17.5%] vs improved inflammation group n = 18 [16.8%], $P = 1.000$), skin rash (persistent inflammation group n = 5 [12.5%] vs improved inflammation group n = 10 [9.3%], $P = .553$), loss of appetite (persistent inflammation group n = 2 [5.0%] vs improved inflammation group n = 0 [0.0%], $P = .073$), kidney injury (persistent inflammation group n = 1 [2.5%] vs improved inflammation group n = 2 [1.9%], $P = .472$), and others (persistent inflammation group n = 5 [12.5%] vs improved inflammation group n = 0 [0.0%], $P = .001$).

Table 2 shows the results of the binomial logistic regression analysis of predictive factors for persistent inflammation. The 5 predictive variables were a WBC count ≥10,000 cells/μL, a CRP level ≥9.0 mg/dL, a large cavity on chest CT, drug-resistant TB infection, and side effects of antituberculous therapy. Cutoff values for WBC count and CRP level were determined by ROC curve analysis. Patients with a large cavity on chest CT had the highest odds ratio, at 8.24 (95% confidence interval [CI]: 3.13–21.7, $P < .001$). A CRP level of 9.0 mg/dL or more was also associated with a high odds ratio, at 4.12 (95% Cl: 1.59–10.7, $P = .004$). The cumulative incidence of the achievement of a low CRP level was analyzed with the Kaplan–Meier method, as shown in Figure 3. The duration to inflammation improvement was longer in patients with large cavities on chest CT than in those without large cavities (log rank test $P < .001$), and the hazard ratio was 2.56 (95% Cl: 1.72–3.81). The median length of hospital stay from admission to achievement of a low CRP level in patients with large cavities was 42 days (IQR 15–69), and that in patients without large cavities was 11 days (IQR 8–20). Patients with a CRP level ≥9.0 mg/dL had a longer time until inflammation improvement than those with a CRP level <9.0 mg/dL (median (IQR) 20 days [13–43] vs 8 days [8–14], log rank test $P < .001$), and the hazard ratio was 2.37 (95% Cl: 1.70–3.30).

Figure 4 shows the relationship between CRP levels and days of hospitalization in patients in the persistent inflammation group (Fig. 4A) and the improved inflammation group (Fig. 4B). In many patients in both groups, CRP levels decreased rapidly after the initiation of antituberculous therapy; however, CRP levels in patients in the persistent inflammation group persisted

Table 1

Baseline characteristics of the study subjects.

	Persistent inflammation group (n = 40)	Improved inflammation group (n = 107)	*P* value
Age, median (IQR), years	67 (58–79)	77 (56–88)	.110
Sex (male/female)	32/8	74/33	.220
Comorbidity, n (%)	32 (80.0)	82 (75.9)	.825
Immunosuppressed status, n (%)	19 (47.5)	33 (30.8)	.081
Smoking history, n (%)*	13 (35.1)	44 (46.3)	.328
Mortality, n (%)	8 (20.0)	18 (16.8)	.635
Duration of hospitalization, median (IQR), day	93 (66–125)	83 (57–112)	.081
Symptomatic status, n (%)	40 (100)	101 (94.4)	.190
Body temperature, median (IQR), degrees	37.8 (36.9–38.9)	37.5 (37.1–38.1)	.244
Acid fast bacillus smear of a sputum (-/±/1+/2+/3+), n	4/3/3/9/21	12/15/5/29/46	.688
Laboratory findings			
WBCs, median (IQR), cells/μL	9,930 (7,398–11,412)	7,730 (6,065–9,900)	.016
CRP, median (IQR), mg/dL	10.8 (9.1–14.5)	8.2 (6.5–12.1)	.002
LDH, median (IQR), IU/L	228 (178–256)	215 (183–282)	.841
Albumin, median (IQR), g/dL	2.37 (2.14–2.72)	2.61 (2.17–3.02)	.050
Classification of pulmonary tuberculosis based on radiography			
Location (right/left/bilateral), n	5/1/34	21/10/79	.203
Properties (I/II/III), n	3/23/14	1/48/58	.015
Spread (1/2/3), n	3/21/16	17/54/36	.232
HRCT findings			
Cavity, n (%)	29 (72.5)	54 (50.5)	.024
Consolidation, n (%)	20 (50.0)	47 (43.9)	.578
Miliary pattern, n (%)	7 (17.5)	16 (15.0)	.799
Severe cavity, n (%)	20 (50.0)	12 (11.2)	<.001
Cheese-like appearance, n (%)	8 (20.0)	14 (13.1)	.307
Pleural effusion, n (%)	13 (32.5)	43 (40.2)	.449
Treatment with recommended regimens, n (%)	26 (65.0)	67 (62.6)	.849
Side effects of antituberculous therapy, n (%)	20 (50.0)	30 (28.0)	.018
History of interruptions in antituberculous therapy, n (%)	9 (22.5)	19 (17.8)	.491
Drug-resistant tuberculosis, n (%)†	5 (12.5)	2 (2.8)	.033
Extrapulmonary tuberculosis, n (%)	9 (22.5)	22 (20.6)	.822
Steroid therapy, n (%)	5 (12.5)	17 (15.9)	.796
Steroid therapy for tuberculosis, n (%)	1 (2.5)	8 (7.5)	.445
Antibiotic therapy for bacteria other than tuberculosis on admission, n (%)	7 (17.5)	23 (21.5)	.653

CRP = C-reactive protein, IQR = interquartile range, LDH = lactate dehydrogenase, WBC = white blood cell.

* Persistent inflammation group n = 37, Improved inflammation group n = 95.

† Persistent inflammation group n = 39, Improved inflammation group n = 106.

above 5 mg/dL and decreased at a slower rate than those in patients in the improved inflammation group. Furthermore, among 144 patients for whom CRP levels were evaluated at 8 weeks after admission, 15 patients (10.4%) had not achieved a low CRP level by week 8 (persistent inflammation for more than 8 weeks group). A large cavity on chest CT was more frequently observed in patients in the persistent inflammation for more than 8 weeks group (n = 10 [31.3%] vs n = 5 [4.5%], $p < 0.001$), with an odds ratio of 9.51 (95% Cl: 2.66–39.2). Among patients in the persistent inflammation for more than 8 weeks group, significant differences between those with sputum culture nonconversion and conversion at 8 weeks were observed (n = 9 [19.1%] vs n = 6 [6.7%], *P* = .042), and sputum culture nonconversion was significantly associated with the presence of a large cavity on CT (large cavity n = 19 [59.4%] vs others n = 28 [26.2%], *P* = .001). In 34 of 137 patients (24.8%), excluding 10 patients who did not achieve a low CRP level during the observational period, the CRP level returned to over 5 mg/dL after a one-time CRP decrease to less than 5 mg/dL. Among those 34 patients, 10 patients had bacterial infection, 9 patients had aspiration pneumonia, 4 patients had side effects of antituberculous therapy, 2 patients stopped antituberculous therapy, 2 patients had digestive diseases, and 1 patient had a paradoxical reaction. The reasons for the secondary increase were unknown in 6 patients; however, their CRP levels had returned to within 5–8 mg/dL on re-evaluation.

Table 2

Binomial logistic regression analysis of predictive factors for persistent inflammation.

		95% confidence interval		
	Odds ratio	Upper limit	Lower limit	*P* value
WBC≥10,000 cells/μL	1.77	0.71	4.42	.224
CRP≥9.0 mg/dL	4.12	1.59	10.7	.004
Large cavity on CT	8.24	3.13	21.7	<.001
Drug-resistant tuberculosis	2.52	0.403	15.8	.322
Side effects of antituberculous therapy	2.65	1.08	6.48	.033

CRP = C-reactive protein, WBC = white blood cells.

4. Discussion

This study demonstrated long-term inflammation in pulmonary TB patients, and 40 of 147 patients (27.2%) who had high or

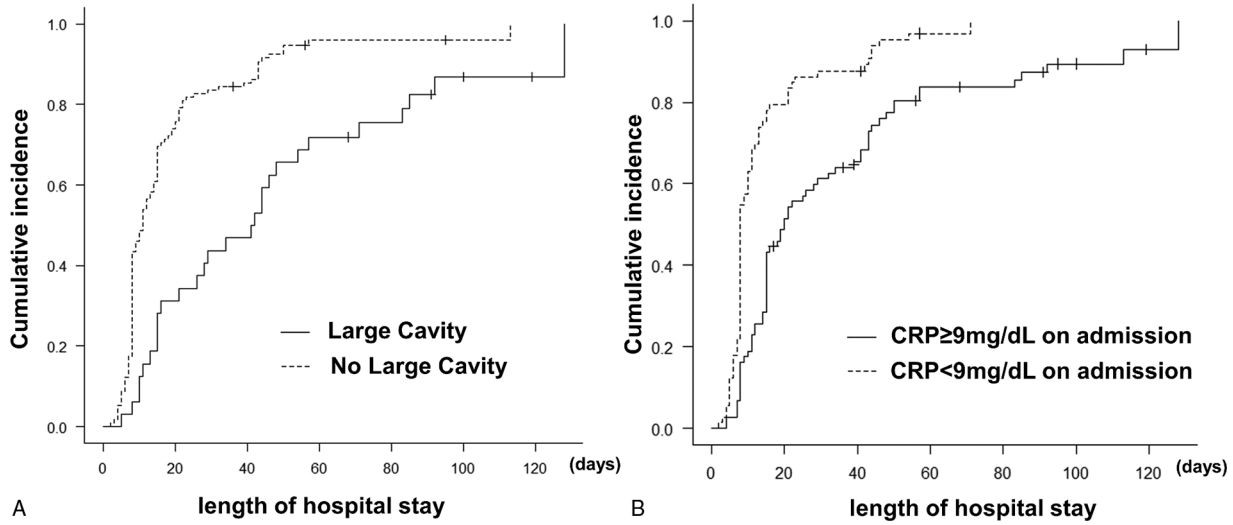

Figure 3. Cumulative incidence of the achievement of low CRP levels based on the Kaplan–Meier method. A: The time to improvement of inflammation was longer in patients with large cavities on CT (log rank test $P < .001$). B: The time to improvement of inflammation was longer in patients with a CRP level ≥9.0 mg/dL (log rank test $P < .001$).

moderate inflammation on admission did not achieve low CRP levels within 4 weeks after admission. The CRP levels in those patients decreased at a slower rate than those in patients in the improved inflammation group; however, the CRP levels in both groups initially decreased rapidly. Patients in the persistent inflammation group showed a higher prevalence of large cavities (cavity diameter ≥4 cm) on chest CT and a higher CRP level on admission. Furthermore, 10.4% of patients had not achieved low CRP levels by week 8, and 66.7% of those patients showed a large cavity on chest CT. Therefore, a large cavity on chest CT and a CRP level ≥9.0 mg/dL on admission were risk factors for persistent severe inflammation. In a patient with a large cavity on chest CT scan and/or a CRP level ≥9.0 mg/dL on admission, long-term inflammation may be observed despite antituberculous therapy if other diseases are ruled out.

Risk factors for persistent severe inflammation in TB patients are unclear, but a previous report showed that a positive sputum culture 2 months after treatment was a risk factor.[4] Our results demonstrated that one risk factor for persistent severe inflammation in TB patients was a large cavity on chest CT, and patients with large cavities tended to show nonconversion of sputum cultures, similar to the findings of a previous report.[13] During the course of TB, a cavity is formed when an expanding granuloma ruptures,[14] and a cavity with a diameter of 4 cm or more is considered a severe lesion.[11] In general, CRP levels are increased in pulmonary TB patients with extensive lung tissue

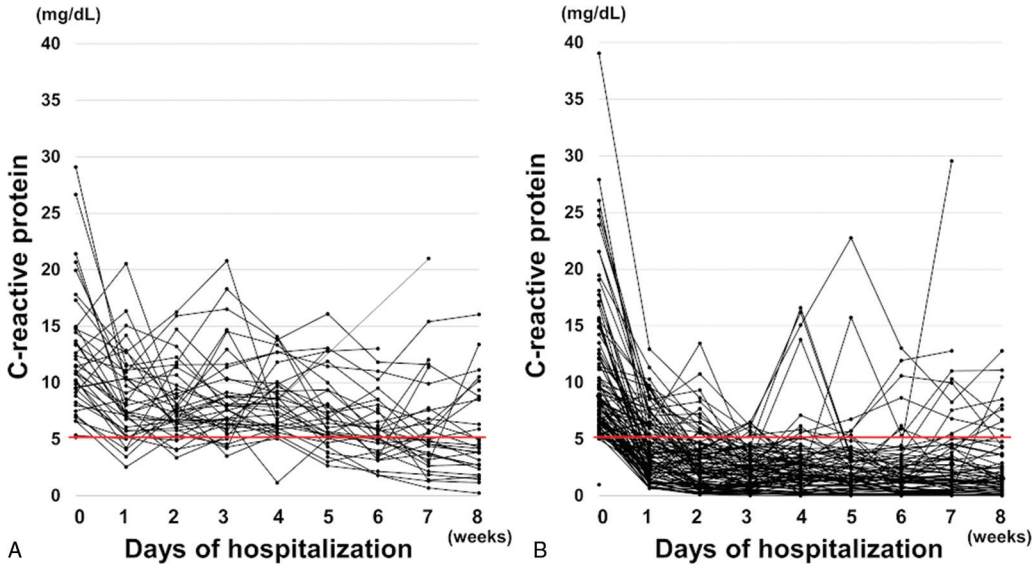

Figure 4. The relationship between CRP levels and days of hospitalization in patients in the persistent inflammation group (A) and the improved inflammation group (B). The red line represents a CRP level of 5 mg/dL.

damage, as the pulmonary inflammatory process is influenced not only by the large population of TB bacilli but also by the presence of lung damage, which is associated with lung tissue inflammation.[3] TB bacilli remaining in a cavity despite antituberculous treatment might induce not only infectious inflammation but also an inappropriate host response to self-antigens, causing autoimmune inflammation.[14] Therefore, the survival of *M. tuberculosis* in a large cavity could cause inflammation to remain high in the long term. According to previous reports that described CRP levels in TB patients, sputum smear grade was associated with the CRP level on admission[3,4]; however, a CRP level of less than 5 mg/dL at 4 weeks was not significantly associated with sputum smear grade on admission in our study.

Autoimmune inflammation in a large cavity might be related to a paradoxical reaction; only 1 patient with persistent severe inflammation in our study was identified as having a paradoxical reaction based on the worsening of existing disease or new TB lesions, with other diseases ruled out during antituberculous therapy.[15] Paradoxical reactions include recurring symptoms, such as fever, and radiological deterioration occurring from 1 week to several months after the initiation of antituberculous treatment.[15] Rapid killing of bacilli with antibiotics may lead to the release of large amounts of microbial components, which can stimulate a strong inflammatory response.[15] A previous report found a median CRP level of 4.5 mg/dL (IQR 2.8–7.4) in patients with paradoxical reactions,[16] for which steroid therapy is recommended for management.[15] Autoimmune inflammation, which might be induced by TB bacilli in a large cavity, is similar to the paradoxical reaction mechanism; therefore, steroid therapy might affect persistent severe inflammation.[15] In our study, one patient received steroid therapy for persistent severe inflammation, and the patient's CRP level and fever rapidly improved. If autoimmune inflammation occurs in a patient with persistent severe inflammation, steroid therapy might be considered.

We also evaluated other risk factors for persistent severe inflammation. A high WBC count; a low albumin level, which is a common cause of immunodeficiency[17,18]; a history of stopping antituberculous medication; and drug-resistant TB are risk factors for mortality in TB patients.[19] However, these variables were not significant risk factors in our study. Regarding antituberculous therapy interruption, only 10 patients stopped antituberculous therapy before achieving a low CRP level, and only 1 of those patients stopped antituberculous therapy after 2 weeks. Many patients with treatment interruption stopped their treatment after an improvement in inflammation or for only a short period; therefore, treatment interruption might not be a cause of persistent severe inflammation. There were significant differences in the side effects of antituberculous therapy between the persistent inflammation group and the improved inflammation group in our study. However, the prevalence of serious side effects, such as liver dysfunction, skin rash, and kidney injury, did not differ significantly. Drug-resistant tuberculosis might be related to high persistent inflammation because of a delay in bacillus killing. Furthermore, patients with miliary TB generally have high mortality (25–30%),[20] but miliary TB did not show a significant relationship with persistent severe inflammation in our study. Adjunctive corticosteroid treatment may be beneficial in treating miliary TB with meningitis, abundant pericardial or pleural effusion, dyspnea, disabling chest pain, and other conditions.[20] Indeed, 6 of 9 patients receiving steroid therapy for TB showed a miliary pattern on chest CT in our study. Therefore, the patients with miliary TB in our study might not have been evaluated accurately because steroids are potent anti-inflammatory agents.[21]

This investigation has several limitations. The study was conducted retrospectively at a single center, and some medical data were not recorded. We recruited patients with moderate-high CRP levels to evaluate the achievement of low CRP levels, and patients with low CRP levels were excluded. Additionally, some patients could not be evaluated at 4 or 8 weeks, and the CRP data were not related to TB alone. For many patients, data were collected at least once per week; however, for some patients, data were collected every 2 weeks after confirmation of improvement in their medical condition.

5. Conclusion

The risk factors for persistent severe inflammation in patients with TB were a large cavity on chest CT (cavity diameter ≥ 4 cm) and a CRP level ≥ 9.0 mg/dL on admission.

Author contributions

Conceptualization: Masafumi Shimoda, Takashi Yoshiyama.
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Methodology: Masafumi Shimoda. Project administration: Masafumi Shimoda, Ken Ohta, Kozo Yoshimori.
Resources: Masafumi Shimoda.
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Visualization: Masafumi Shimoda.
Writing – original draft: Masafumi Shimoda.
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