Original Article

INVESTIGATION OF POTENTIAL PROGNOSTIC FACTORS FOR THE INCREASINGLY PREVALENT MILIARY TUBERCULOSIS IN JAPAN

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Abstract [Objectives] Although the prevalence of tuberculosis has been decreasing in Japan, the prevalence of miliary tuberculosis (TB) has been gradually increasing. Therefore, it would be important that we know prognostic factors for miliary TB to provide suitable treatment and general management. To identify prognostic factors, we retrospectively studied 106 cases of miliary TB in our hospital. [Methods] We reviewed the medical records of 106 patients who had been diagnosed with miliary TB and undergone in-hospital treatment at our medical institution between April 2004 and March 2013. We conducted retrospective comparative analyses of age, sex, smoking history, complications, history of immunosuppressant use, presence or absence of hypoxemia, Eastern Cooperative Oncology Group Performance Status (PS), blood cultures, blood tests, administration of rifampicin (RFP) and isoniazid (INH), and time delay from symptom presentation to diagnosis between the patients who survived and were discharged (survivor group) and those who died in hospital (non-survivor group). In addition, we examined factors which contributed to longer survival period. [Results] The patients in the non-survivor group (n=41) were older and less nourished and had poorer oxygenation, poorer PS, and smaller number of peripheral blood lymphocyte count than the patients in the survivor group (n=65). And the rate of administration of RFP in the non-survivor group was lower than that in the survivor group. Administration of RFP was related to the longer survival time in the non-survivor group. [Conclusions] Nutritional status, oxygenation, PS, peripheral blood lymphocyte count, and RFP administration were identified as prognostic factors of miliary TB. Administration of RFP appeared to be most important for the survival.

Key words: Miliary tuberculosis, Prognostic factors, Rifampicin, Lymphocyte count

INTRODUCTION

Miliary tuberculosis is a hematogenously disseminated type of tuberculosis, which involves active tuberculosis lesions identified bacteriologically or pathologically in at least two organs and diffuse nodular satellite lesions equivalent or close in size to grains of millet[1]. The most frequently affected organs are the lung, liver, and spleen, but the kidney, bone marrow, brain, and other organs in any part of the body can be affected. Because the disease can affect multiple organs, delayed diagnosis can be fatal; thus, early detection is critical. However, early diagnosis is often difficult because symptoms vary considerably depending on the organs affected.

Although the prevalence of tuberculosis has been decreasing in Japan, the prevalence of miliary tuberculosis has been gradually increasing (Fig. 1). In the 2016 statistics, 633 cases of miliary tuberculosis were registered in Japan, which corresponds to 0.50 incidences per 100,000 people and accounts for 15.8% of extrapulmonary tuberculosis cases[2]. In other countries, of all patients with tuberculosis, 1.5% and 2.7% were estimated to have miliary tuberculosis in the US and in the European Union/European Economic Area (EU/EEA), respectively[3][4]. It appears that miliary tuberculosis may be found in a certain population at the present time when prevalence rate of tuberculosis is decreasing.

In spite of the critical importance of identifying prognostic factors (factors related to in-hospital death) for providing appropriate treatment and general care to the patients with

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miliary tuberculosis, no previous studies have investigated these factors in more than 100 patients with miliary tuberculosis. Besides, we would expect that increased frequency of immunosuppressant medication and aging of society these days might modify prognostic factors of miliary tuberculosis, particularly in developed countries. We, therefore, conducted this study with more than 100 patients to identify current prognostic factors of miliary tuberculosis.

METHODS

Sample collection

There were 222 patients who had been clinically diagnosed with miliary tuberculosis and admitted to our hospital between April 2004 and March 2013. In this study, we defined miliary tuberculosis as a hematogenously disseminated type of tuberculosis, which involves active tuberculosis lesions identified bacteriologically or pathologically in at least two organs, and which shows chest X-ray findings indicating diffuse nodular satellite lesions equivalent or close in size to grains of millet (approximatory 1−5 mm)[1] in all lung fields. We excluded patients with pulmonary tuberculosis exhibiting miliary shadows on chest X-ray or chest computed tomography (CT), but without evidence of extrapulmonary tuberculosis, *i.e*. isolation of *Mycobacterium tuberculosis* from more than one samples or tissues, other than tuberculous pleuritis or lymphadenopathy. Among 222 inpatients during that period, 106 patients met the criteria (Fig. 2). Their medical records were evaluated retrospectively to extract age, sex, smoking history, complications, administration of immunosuppressant, presence or absence of hypoxemia, Eastern Cooperative Oncology Group Performance Status (PS), history and results of blood culture test, and various blood test items [peripheral blood lymphocyte count, hemoglobin (Hb), albumin (Alb), alkaline phosphatase (ALP), and C-reactive protein (CRP)].

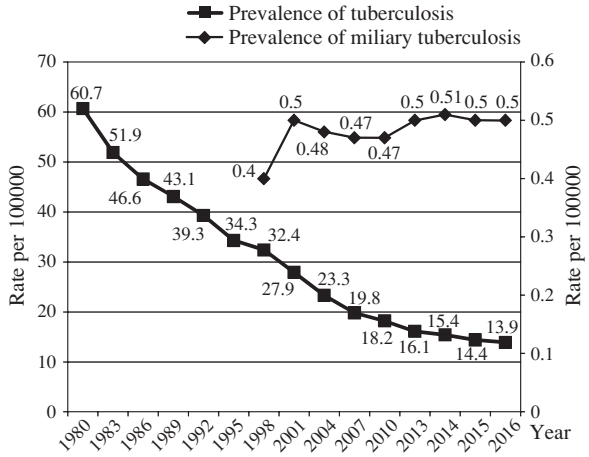

Fig. 1 This figure shows the prevalence of tuberculosis and that of miliary tuberculosis in Japan per 100,000 populations. (adapted from Japan Anti-Tuberculosis Association: Statistic of TB 2017)

Evaluation

We evaluated complications, PS, presence or absence of hypoxemia, and CRP as markers of general conditions and Hb and Alb as markers of nutrition. In addition, administration of immunosuppressant or peripheral blood lymphocyte counts were assessed to evaluate the immune status of the patients with miliary tuberculosis. We included ALP as one of the evaluation items because high ALP is often observed in patients with miliary tuberculosis, possibly due to liver involvement in miliary tuberculosis[5)−7)]. We also checked administration of rifampicin (RFP) and isoniazid (INH), because these two drugs are considered as the key drugs in the treatment of tuberculosis. Furthermore, we checked drug resistance of *M.tuberculosis* and interval from symptom presentation to the diagnosis.

Statistical analysis

A total of 106 patients were divided into two groups; those who had survived and been discharged (survivor group) and those who had died in the hospital (non-survivor group). The abovementioned factors were compared between the two groups using the t-test or χ-square test. For the factors that showed a significant difference between the survivor group and non-survivor group, we analyzed correlation with survival in days in the non-survivor group by univariate and multivariate survival analysis. Multivariate survival analysis was conducted using the Cox proportional hazards model to identify independent prognostic factors.

This study was reviewed and approved by the ethics committee of the National Hospital Organization Tokyo National Hospital, and was conducted according to the principles expressed in the Declaration of Helsinki.

RESULTS

The survivor and non-survivor groups included 65 and 41 patients, respectively. In the non-survivor group, the mean age was higher (76.5±2.1 vs. 65.0±2.5 years, p=0.002), the proportion of PS4 was greater (63.4% vs. 27.7%, p=0.0028), the rate of having concomitant hypoxemia was

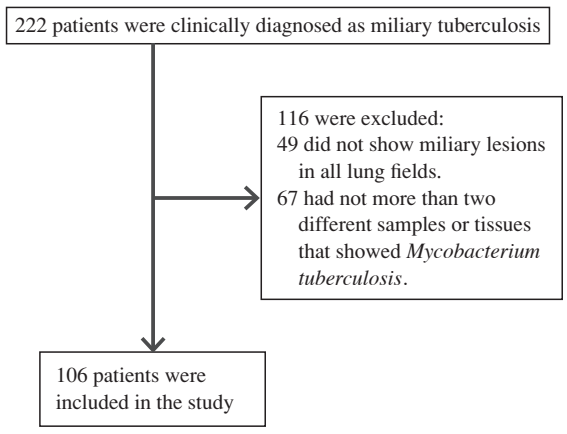

Fig. 2 Flow diagram of patients included in the study

Table 1 Comparison of clinical factors of survivors with non-survivors

Evaluation items	Survivors (n=65)	Non-survivors (n=41)	p-value
Age	65.0±2.5 y.o	76.5±2.1 y.o	p=0.002
Male : Female	31 : 34	17 : 24	p=0.55
PS 4	18 (27.7%)	26 (63.4%)	p=0.0028
Hypoxemia (SpO_2 <90%)	18 (27.7%)	28 (68.3%)	p<0.001
Immunosuppressive agents and biologics	11 (16.9%)	7 (17.1%)	p=1.00
Albumin	2.6±0.08 g/d*l*	2.1±0.06 g/d*l*	p<0.001
Hemoglobin	11.1±0.23 g/d*l*	10.4±0.31 g/d*l*	p=0.07
LDH	360.3±27.2 IU	391.4±30.0 IU	p=0.45
ALP	547.0±59.0 IU	408.8±35.1 IU	p=0.09
CRP	17.0±9.3 mg/d*l*	11.9±1.3 mg/d*l*	p=0.66
Lymphocytes	707.2±71.4 /μl	389.0±42.7 /μl	p=0.001
Administration of RFP	64 (98.5%)	29 (70.7%)	p<0.001
Administration of INH	63 (96.9%)	36 (87.8%)	p=0.07
Tuberculous meningitis	7 (10.8%)	1 (2.4%)	p=0.15
Period of up to diagnosis	6.8±1.1 weeks	6.1±1.0 weeks	p=0.72
Comorbidity			
HIV infection	6 (9.2%)	1 (2.4%)	p=0.24
Malignant disease	4 (6.2%)	3 (7.3%)	p=1.00
Chronic heart failure	1 (1.5%)	2 (4.9%)	p=0.56
Diabetes mellitus	9 (13.8%)	7 (17.1%)	p=0.78
Connective tissue disease and relative disease	10 (15.4%)	5 (12.2%)	p=0.78

Abbreviations: PS, performance status

higher (68.3% vs. 27.7%, p<0.001), the mean Alb level was lower (2.1±0.06 g/d*l* vs. 2.6±0.08 g/d*l*, p<0.001), and the mean peripheral blood lymphocyte count was lower (389.0±42.7/μl vs. 707.2±71.4/μl p=0.001) (Table 1). Although it was high in both groups, the ALP level was not significantly different between the two groups. In addition, no significant differences were noted in the rates of the use of immunosuppressants/biologicals. RFP had been administered to 64 of 65 patients in the survivor group (98.5%) and to 29 of 41 patients in the non-survivor group (70.7%), indicating a statistically significant difference (p<0.001). On the other hand, INH had been used in 63 of 65 patients in the survivor group (96.9%), and in 36 of 41 patients (87.8%) in the non-survivor group, without significant difference between the two groups (p=0.07).

Because the smoking history was unknown for many patients in both groups, an intergroup comparison could not be made. There were no differences in the rate of major comorbidities. We detected no differences in the rate of HIV infection, malignant diseases, chronic obstructive pulmonary disease, chronic heart disease, diabetes mellitus, and connective tissue diseases and the related diseases between the two groups. Of 106 patients, 66 (45 in the survivor group and 21 in the non-survivor group) had undergone blood culture. The blood culture positive rates for *M.tuberculosis* in the survivor and non-survivor groups were 15.6% and 28.6%, respectively, without significant difference. We could not evaluate drug resistance of *M.tuberculosis* between the two groups, because it could not be available in 10 of 41 cases in the non-survivor group (Table 2). The length of time to diagnosis from symptom expression was about 6 weeks in the both groups and there was no significant difference (p=0.72).

Table 2 Drug susceptibility

Resistant drug	Survivors (n=65)	Non-survivors (n=31**)
Rifampicin	0 (0%)	0 (0%)
Isoniazid	3 (4.6%)*	0 (0%)
Ethambutol	0 (0%)	0 (0%)
Streptomycin	6 (9.2%)*	3 (9.7%)
Pyrazinamide	2 (3.1%)	1 (3.2%)
Ethionamide	1 (1.5%)*	0 (0%)

*No one showed susceptibility to isoniazid only, 3 cases showed susceptibility to streptomycin only, 2 cases showed susceptibility to isoniazid and streptomycin, and one case showed susceptibility to isoniazid, streptomycin and ethionamide.
**10 cases' drug susceptibilities of non-survivors could not be available.

We conducted univariate analyses to check contribution of each clinical factor to the survival period in non-survivors, and multivariate analysis to identify independent prognostic factors using the Cox proportional hazards regression model. The univariate analyses suggested that only RFP administration was related to the survival period of non-survivors (Fig. 4-(C)). PS (Fig. 4-(A)), serum albumin level (Fig. 3-(B)), peripheral blood lymphocyte count (Fig. 3-(C)), or oxygen desaturation (Fig. 4-(B)) did not affect the survival period. Multivariate survival analysis revealed RFP administration was related to the longer survival time (HR, 4.51; p=0.0007; 95% confidential interval [CI], 1.89−10.76). Although the

survival period was also affected by age (HR, 0.97; p＝0.02; 95％CI, 0.94−1.00), there was no correlation between age and survival period in non-survivor when we checked Pearson's product-moment correlation coefficient (p＝0.70, r＝0.062) (Fig. 3-(A)).

DISCUSSION

Some published reports of clinical studies conducted in miliary tuberculosis patients in Japan have included comparative analyses on potential prognostic factors, including blood tests, history of tuberculosis, chest radiographs, and complications, and have noted chest X-ray findings and nutritional status as prognostic factors[8)−12)]. However, no previous studies have investigated the association of a large array of factors, including respiratory status (hypoxemia), PS, and TB treatment. We investigated those factors and identified administration of RFP as the most important prognostic factor. Other factors, such as advanced age, PS4, hypoxemia, low peripheral blood lymphocyte count, were also related to the poor prognosis. The higher rates of patient with PS4 or with hypoxemia in the non-survivor group might indicate seriousness of miliary tuberculosis at the time of diagnosis,

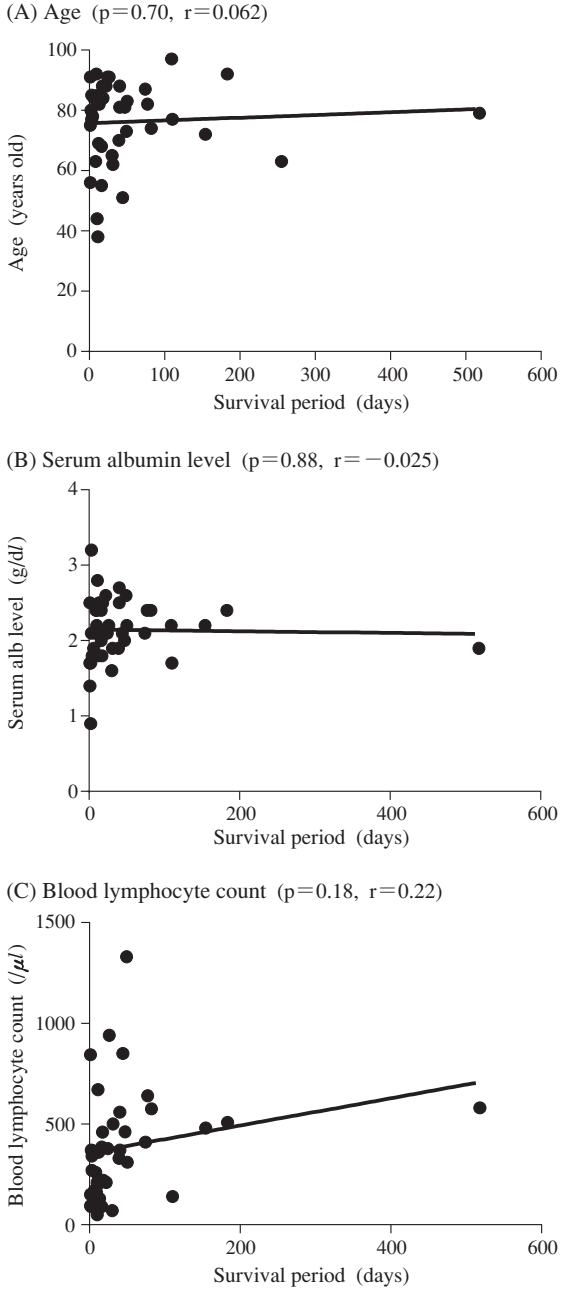

Fig. 3 Correlation between survival period and age (A), serum albumin level (B), blood lymphocyte count (C) in non-survivor group.

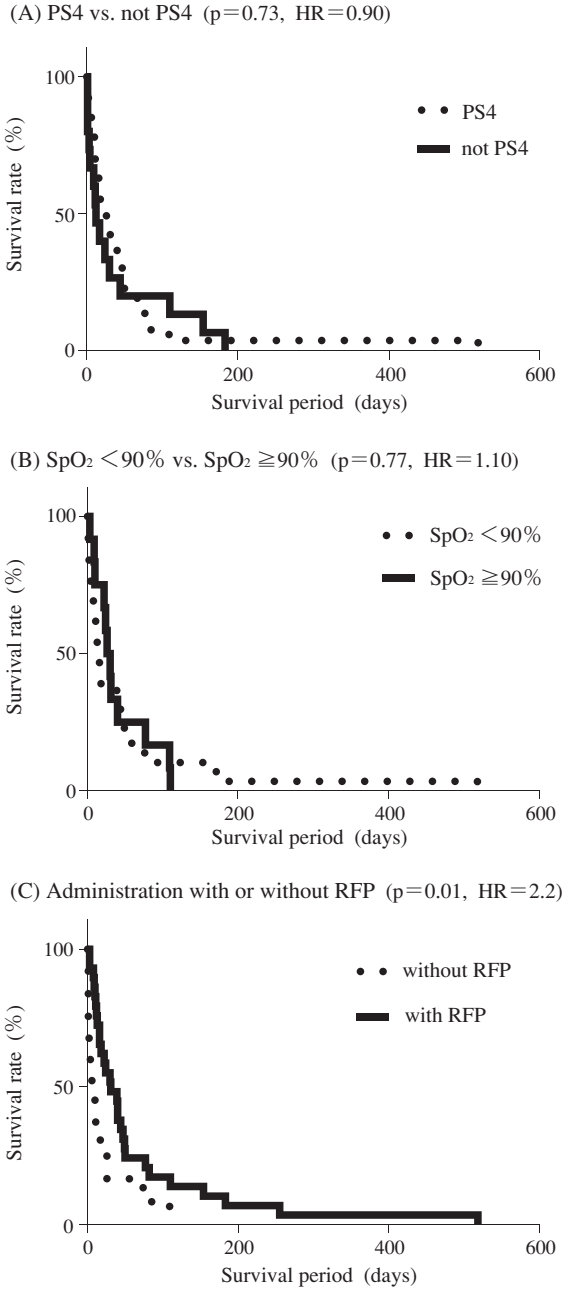

Fig. 4 Comparison of survival curves in non-survivor group. Correlation between survival period and PS (A), oxygen desaturation (SpO_2) (B), RFP administration (C).
Abbreviations: PS, performance status; RFP, rifampicin.

and also rapid worsening of tuberculosis after the diagnosis.

Because of the increased risk of developing tuberculosis during the administration of a biological product, patients should undergo screening for tuberculosis prior to receiving any biologicals and receive INH if latent tuberculosis infection (LTBI) was suggested[13)-16)]. The results from the present study showed no significant differences in the rates of the use of biologicals or immunosuppressive agents between the two groups. It could be because the patients might recover from immunocompromised status by discontinuation of biologicals or immunosuppressive agents, or because patients who are treated with these drugs might have been in good conditions and under the close surveillance. However, we should mention that screening for tuberculosis, LTBI treatment when needed, and early diagnosis and adequate treatment after onset are very important when using biologicals and immunosuppressants[12)-16)].

Regarding malnutrition and peripheral blood lymphocyte count, Hiratsuka et al. have reported that patients with miliary tuberculosis have a poorer nutritional status and a lower peripheral blood lymphocyte count than those with other types of tuberculosis[8)]. In addition, some reports have linked malnutrition and reduced peripheral blood lymphocyte count with increased severity and prognosis of tuberculosis[9)-11)]. Our results indicated that these factors were also associated with the prognosis of miliary tuberculosis. Jones et al. reported a positive correlation between serum Alb levels and CD4 lymphocyte counts[11)]. By improving the nutritional status of tuberculosis patients, an increase in CD4 lymphocytes might be expected, which in turn will contribute to preventing tuberculosis from worsening, thereby improving prognosis.

Similar to pulmonary tuberculosis, miliary tuberculosis is primarily treated with INH, RFP, and ethambutol (EB), which are combined with PZA when the patient is not elderly, does not have liver dysfunction, and can ingest oral drugs[17)]. If PZA is difficult to be administered, a three-drug regimen consisting of INH, RFP, and EB is used for treatment[17)]. In this study, we investigated the correlation of tuberculosis treatment and prognosis, especially INH and RFP administration, and found that administration of RFP was significantly higher in the survivor group whereas that of INH was not significantly different between the two groups. It suggested that RFP is the most essential drug for the treatment of tuberculosis.

When we conducted a multivariate survival analysis with factors related to the general conditions (serum albumin level, peripheral blood lymphocyte count, oxygen desaturation and PS) and tuberculosis treatment (administration of RFP), treatment with RFP was the only independent factor which could prolong the survival period. The patients who had not received RFP were those with complications of liver dysfunction or those with difficulties in ingestion. Based on this result, we should administer RFP even when patients couldn't take medicines orally. In Japan, where injectable RFP is not available, RFP might be administered through a nasogastric tube. In this study, 10 of 12 cases that had not received RFP in non-survivor group exhibited hypoxemia. In such cases, insertion of nasogastric tube might be waived, giving priority to oxygen administration. Although injectable INH, SM, and levofloxacin were often used for these patients, RFP would have been administered without hesitation to the patients if an injectable RFP formulation were available in Japan.

In this study, there were several limitations. One of them was that blood culture tests weren't conducted in all cases, so we did not evaluate positive rate of *M.tuberculosis* in blood culture tests as a prognostic factor. Another limitation was that inserting a nasogastric tube in severe cases was largely at the discretion of the attending physician in our institution, and there might be a selection bias in RFP administration. In addition, drug resistances of *M.tuberculosis* in some of the non-survivor cases were not known. A choice of drug combination could be also very important in case of drug-resistant tuberculosis.

In conclusion, the results of this study demonstrated the importance of administration of RFP in treatment of miliary tuberculosis. We think RFP administration could increase the survival of the patients with miliary tuberculosis. If we could use injectable RFP in Japan, more patients with miliary or severe tuberculosis, unable to take medicines orally or to apply a nasogastric tube, could be rescued.

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日本で増加傾向にある粟粒結核の予後因子の検討

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要旨：〔目的〕粟粒結核における予後因子（死亡退院に関連する因子）を検討するため，われわれは当院における粟粒結核症例106例を後方視的に調査した。〔方法〕当院で2004年4月から2013年3月までに粟粒結核の診断で入院・加療された106例の診療記録を後方視的に評価し，年齢，性別，喫煙歴，合併症，免疫抑制剤使用歴，低酸素血症の有無，performance status（PS），血液培養施行歴とその結果，各種血液検査項目，isoniazid（INH）およびrifampicin（RFP）投与歴，結核菌の薬剤感受性，および症状発現から診断までの期間を観察項目とし，生存退院群（生存群），死亡退院群（死亡群）に分け，比較・検討した。また，生存期間延長に寄与する因子についても検討した。〔結果〕生存群（65例）に比べ死亡群（41例）は高齢，低栄養，酸素化不良，PS不良，末梢血リンパ球数低値であった。また，RFP投与率は死亡群で低かった。さらに，死亡群においてRFP投与歴は有意に生存期間を延長した。〔結論〕粟粒結核の予後には栄養状態，酸素化，PS，末梢血リンパ球数，RFP投与の有無が関与している可能性があり，RFP投与の有無は特に重要な因子であると考えられた。
キーワーズ：粟粒結核，予後因子，リファンピシン，リンパ球数