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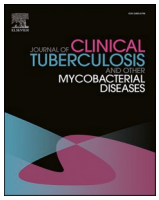

Monocytes predict prognosis and successful treatment in older patients with miliary tuberculosis

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ABSTRACT

Background: The increasing number of patients with miliary tuberculosis (MTB) is a concern in an aging society because of its high mortality rate. Several prognostic biomarkers for MTB have been identified; however, the predictive ability of monocytes as biomarkers remains unknown. This study demonstrates the usefulness of monocytes as prognostic biomarkers for MTB.

Materials and methods: We retrospectively compared the clinical findings of 52 patients with MTB hospitalized between April 2013 and October 2021. The predictive ability of biomarkers for 3-month prognosis and their cutoff values were calculated. Survival times and longitudinal changes in monocytes after initiating treatment were compared.

Results: A smaller number of monocytes (#M), higher lymphocyte-monocyte ratio (LMR), higher neutrophil-monocyte ratio, and poorer performance status were associated with death within 3 months. #M was an independent prognostic factor. #M and LMR exhibited the highest predictive performance compared to others using receiver operating characteristic curve analysis (area under the curve = 0.86 and 0.85, respectively). Survival time was shorter in patients with #M $\leq$ 200 cells/μL and LMR $>$ 2.5. Rapidly increasing #M after treatment was related to better prognosis in patients with #M $\leq$ 200 cells/μL at diagnosis.

Conclusions: #M at diagnosis and longitudinal changes in monocytes are related to MTB prognosis.

1. Background

An increasing number of older patients with tuberculosis (TB) and their high mortality have been reported in an aging society [1]. In particular, the growing number of patients with miliary TB (MTB), a rare and fatal infectious disease, is a concern. MTB is caused by massive lymphohematogenous dissemination of *Mycobacterium tuberculosis* and often results in life-threatening conditions such as acute respiratory distress syndrome (ARDS) [2–5]. The high mortality rate of MTB is well known at approximately 30–65% [2–7], and the mortality rate in older patients has been reported to be even higher [6,8,9].

It is important to investigate the prognostic risk factors for appropriate management. To date, many studies on MTB have revealed prognostic factors such as old age, nutritional status, serum albumin, sodium, blood urea nitrogen (BUN), ARDS, and neutrophil–lymphocyte ratio (NLR) [2–11]. However, there are no reports on biomarkers containing monocytes, although the immune response against *Mycobacterium tuberculosis* accelerates the recruitment of peripheral blood monocytes for the formation of caseating granulomas in infectious lesions [12–17]. Some studies have reported that biomarkers containing monocytes are useful for predicting the onset of active TB and for the successful treatment of TB [18,19]. Nevertheless, the prognostic ability of monocytes as biomarkers remains unknown.

This study aimed to demonstrate the predictive ability of monocytes as biomarkers for the prognosis of patients with MTB.

2. Materials and methods

2.1. Patients and clinical data

We retrospectively analyzed the medical records of 64 patients with MTB who were hospitalized at Kobe City Nishi-Kobe Medical Center

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between April 1, 2013, and October 31, 2021. Of these, 52 patients were enrolled in our study, and 12 patients were excluded due to the following reasons: insufficient clinical data on white blood cell (WBC) count (N = 7), active blood cancer or human T-cell leukemia virus type 1 infection (N = 2), terminal stage of cancer (N = 1), different diagnosis (N = 1), and treatment began before the first available data (N = 1) (Supplementary Fig. 1).

We collected the clinical records of 52 patients at diagnosis, including age, sex, clinical history, smoking status, body mass index (BMI), performance status (PS), symptoms, drug resistance, smear status of *Mycobacterium tuberculosis*, use of immunosuppressive agents, therapeutic regimens, interval from diagnosis to treatment, available laboratory data, and overall survival. The patients were dichotomized into two groups: death within 3 months (N = 15) and survival at 3 months (N = 37). Biomarkers related to prognosis were investigated, and their predictive ability was evaluated. The patients were then divided into subgroups based on the cutoff value of each promising biomarker to evaluate survival time. The 3-month and 1-year survival times were defined as the duration from the date of therapy initiation until the end of each follow-up time or the date of death from any cause. The follow-up period was 1 year. Data cutoff was conducted on October 31, 2022.

This study was approved by Kobe City Nishi-Kobe Medical Center Ethics Committee (approval number: 2022–25). The requirement for informed consent for the use of clinical information was waived because of the retrospective study design. However, all patients were guaranteed opportunities to know and withdraw from this study by notification.

2.2. Diagnosis of MTB

MTB was diagnosed based on the following three criteria. The first category, which was evaluated by two pneumologists, was computed tomography of the lungs with bilateral miliary and random nodules. The second category was positive acid-fast bacilli smear, polymerase chain reaction, or culture for *Mycobacterium tuberculosis* from clinical specimens such as sputum, urine, cerebrospinal fluid, stomach, or pleural fluid. The third category was the radiological improvement of the bilateral pulmonary nodules after treatment commencement.

2.3. Statistical analyses

Continuous variables were analyzed using Student's *t*-test or Mann–Whitney *U* test. Dichotomous variables were analyzed using the chi-squared test. The promising biomarkers found in the univariate analyses were evaluated using the Cox proportional hazards model for 3-month and 1-year survival. The area under the curve (AUC) was calculated using receiver operating characteristic (ROC) analysis to compare the predictive ability of the promising biomarkers. A test with an AUC of 0.7–0.9 was considered moderately accurate compared with an AUC of 0.5–0.7. The cutoff values for predicting prognosis were determined for the promising biomarkers, and patients were divided into two subgroups. One-year Kaplan–Meier survival curves of the two subgroups were compared using the log-rank test. In addition, we investigated longitudinal changes in the number of monocytes (#M), lymphocytes

Table 1
Patient characteristics.

Characteristics	Total (%) (N = 52)	Death within 3 months (%) (N = 15)	Survival at 3 months (%) (N = 37)	p
Age (years)				
Mean (SD)	83 (13.7)	85 (9.8)	82 (14.9)	0.42
Sex				
Male	19 (36.5)	6 (40.0)	13 (35.1)	0.74
Female	33 (63.5)	9 (60.0)	24 (64.9)	
Clinical history				
Tuberculosis	11 (21.2)	5 (33.3)	6 (16.2)	0.26
Diabetes mellitus	14 (26.9)	6 (40.0)	8 (21.6)	0.19
Chronic kidney disease	19 (36.5)	5 (33.3)	14 (37.8)	1.00
Dialysis	5 (9.6)	1 (6.7)	4 (10.8)	1.00
Cancer	9 (17.3)	4 (26.7)	5 (13.5)	0.42
Smoking status				
Never	32 (61.5)	10 (66.7)	22 (59.5)	0.24
Current or former	11 (21.2)	1 (6.7)	10 (27.0)	
Unknown	9 (17.3)	4 (26.7)	5 (13.5)	
BMI (kg/m^2)[a]				
Mean (SD)	20.5 (4.8)	18 (4.3)	20.9 (4.8)	0.20
PS				
4	29 (55.8)	13 (86.7)	16 (43.2)	<0.01
1–3	23 (44.2)	2 (13.3)	21 (56.8)	
Symptoms				
Fever	36 (69.2)	9 (60.0)	27 (73.0)	0.51
Dyspnea	21 (40.4)	8 (53.3)	13 (35.1)	0.35
Cough	9 (17.3)	2 (13.3)	7 (18.9)	1.00
Loss of appetite	21 (40.4)	9 (60.0)	12 (32.4)	0.12
Fatigue	22 (42.3)	9 (60.0)	13 (35.1)	0.13
Drug resistance*	4 (9.1)	1 (10)	3 (8.8)	1.00
Positive smear for *Mycobacterium tuberculosis*	47 (90.4)	14 (93.3)	33 (89.2)	1.00
Immunosuppressive agents	13 (25.0)	2 (13.3)	11 (29.7)	0.30
Therapeutic regimen				
HRE**	22 (42.3)	5 (33.3)	17 (45.9)	1.00
HREZ***	21 (40.4)	4 (26.7)	17 (45.9)	
Others****	9 (17.3)			
Interval from diagnosis to treatment				
Median (IQR), days	2 (1–5)	2.5 (1–5.75)	2 (1–5)	0.87

*Forty-four patients underwent drug-sensitivity testing for *Mycobacterium tuberculosis*. **HRE represents isoniazid, rifampicin, and ethambutol. ***HREZ represents isoniazid, rifampicin, ethambutol, and pyrazinamide. ****Others mainly contained regimens of HRE and fluoroquinolone, such as levofloxacin and moxifloxacin. [a]The body height of one patient was unknown, and 51 patients were compared.
SD, standard deviation; BMI, body mass index; PS, performance status; IQR, interquartile range.

(#L), and lymphocyte-monocyte ratio (LMR) in patients with #M ≤200 cells/μL for 3 weeks after initiating treatment. The first day of treatment was considered as day 1. The laboratory data before and after one day from days 8, 15, and 22 were treated as the data on days 8, 15, and 22, respectively, and compared with the data at diagnosis using the paired *t*-test. A two-tailed P-value of less than 0.05 indicated statistical significance. All statistical analyses were performed using JMP 16 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Fifty-two patients were included in the final analysis, and their parameters were compared between the groups of death within 3 months and survival at 3 months (Table 1). Fifteen of 52 patients died within 3 months and during hospitalization. None of the parameters were statistically significant, except for PS ($p < 0.01$). In this study, almost all patients were older, with a mean age of 83 years. Approximately one-third of the patients in both groups were female. The proportion of patients with a history of TB was 21.2 %, and the most frequent clinical histories were chronic kidney disease and diabetes mellitus (36.5 % and 26.9 %, respectively). Fever was the most common symptom (69.2 %), followed by dyspnea, loss of appetite, and fatigue (40.4 %, 40.4 %, and 42.3 %, respectively). BMI in the group of death within 3 months was smaller than that in the counterpart group (18.0 and 20.9, respectively); however, the difference was not statistically significant. The positive ratio in sputum smear and culture for *Mycobacterium tuberculosis* was almost the same, and the ratio of *Mycobacterium tuberculosis* with drug resistance was not different between the two groups (10 % and 8.8 %, respectively). There were no differences in the therapeutic regimens. The median interval from diagnosis to treatment initiation was 2 days, without a significant difference.

3.2. Laboratory findings at diagnosis

The laboratory data at diagnosis are summarized in Table 2. The number of WBCs, neutrophils, #L, #M, and platelets showed a statistically significant decrease in the group of death within 3 months compared with their counterpart ($p = 0.006$, 0.046, 0.002, <0.001, and 0.002, respectively). The LMR and neutrophil-monocyte ratio (NMR) were significantly different between the two groups ($p < 0.001$ and $p = 0.003$, respectively); however, there was no difference in NLR. The BUN levels also showed a statistically significant difference ($p = 0.013$). Significantly higher C-reactive protein levels were found in the group of death within 3 months ($p = 0.039$); however, this parameter was collected from 51 patients because of insufficient laboratory data. The parameters related to liver function and serum sodium concentration did not differ.

3.3. Parameters related to 3-month and 1-year survival

Parameters identified as significant variables from univariate analyses were selected based on smaller p-values for patient characteristics and laboratory data because of the limited number of participants in this study. #M and PS were independent predictive factors for 3-month survival ($p = 0.005$ and 0.037, respectively), and #M was an independent predictive factor for 1-year survival ($p = 0.003$) using the Cox proportional hazards model (Table 3).

3.4. AUC and cutoff values

We analyzed the predictive ability of #M and PS by drawing ROC curves and found that the AUCs were 0.86 and 0.72, respectively (Fig. 1a, 1b). The cutoff value of #M to predict patient prognosis was determined to be 200 cells/μL. We additionally analyzed the predictive ability of LMR and NMR because of their smaller p-values, and their

Table 3
Results of the Cox proportional hazards model adjusted for sex and age to determine prognostic factors for 3-month and 1-year survival.

Parameters	3-month survival		1-year survival	
	HR (95 % CI)	p	HR (95 % CI)	p
Sex	0.944 (0.314–2.840)	0.920	1.006 (0.959–1.063)	0.341
Age	0.984 (0.920–1.016)	0.641	1.006 (0.959–1.063)	0.830
#M	0.989 (0.979–0.999)	0.005	0.994 (0.989–0.998)	0.003
#L	1.002 (0.999–1.005)	0.214	1.002 (1.000–1.004)	0.106
platelets	1.014 (0.912–1.126)	0.802	0.989 (0.918–1.064)	0.774
PS	3.079 (0.831–11.41)	0.037	2.004 (0.971–4.805)	0.061

#M, number of monocytes; #L, number of lymphocytes; PS, performance status; HR, hazard ratio; CI, confidence interval.

Table 2
Laboratory findings of the patients with miliary tuberculosis.

Laboratory findings	Total (N = 52)	Death within 3 months (N = 15)	Survival at 3 months (N = 37)	p
WBCs, /μL	5370 ± 2379	3800 ± 1754	5755 ± 2497	0.006
Neutrophils, /μL	4300 ± 2160	3328 ± 1674	4619 ± 2313	0.046
#L, /μL	490 ± 335	323 ± 192	572 ± 347	0.002
#M, /μL	198 ± 243	84 ± 58	389 ± 244	<0.001
NLR	8.8 ± 10.6	9.8 ± 10.8	8.0 ± 10.4	0.176
NMR	17.0 ± 30.6	41.9 ± 33.3	14.8 ± 26.0	0.003
LMR	2.1 ± 1.9	3.3 ± 2.8	1.7 ± 1.0	<0.001
Hb, g/dL	11.4 ± 4.1	11.5 ± 2.4	11.4 ± 4.8	0.746
platelets, $\times 10^4$/μL	17.8 ± 9.8	12.75 ± 7.0	19.4 ± 9.7	0.002
Total protein*, g/dL	6.1 ± 0.9	5.5 ± 0.8	6.3 ± 0.9	0.099
AST	33.5 ± 66.7	43 ± 112	31 ± 73	0.053
ALT	22 ± 51	21 ± 89	23 ± 60	0.584
BUN, mg/dL	32 ± 30	46 ± 39	25 ± 22	0.013
Cre, mg/dL	1.2 ± 2.3	1.3 ± 2.0	1.1 ± 2.4	0.980
CRP**, mg/dL	6.7 ± 6.1	8.8 ± 7.5	5.5 ± 5.1	0.039
Na, mEq/L	136.0 ± 5.6	135.0 ± 6.7	136.0 ± 5.0	0.161

All data are presented as mean ± standard deviation. *Forty-six patients were analyzed. **Fifty-one patients were analyzed.
WBCs, white blood cells; #L, number of lymphocytes; #M, number of monocytes; NLR, neutrophil–lymphocyte ratio; NMR, neutrophil-monocyte ratio; LMR, lymphocyte-monocyte ratio; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; Na, sodium.

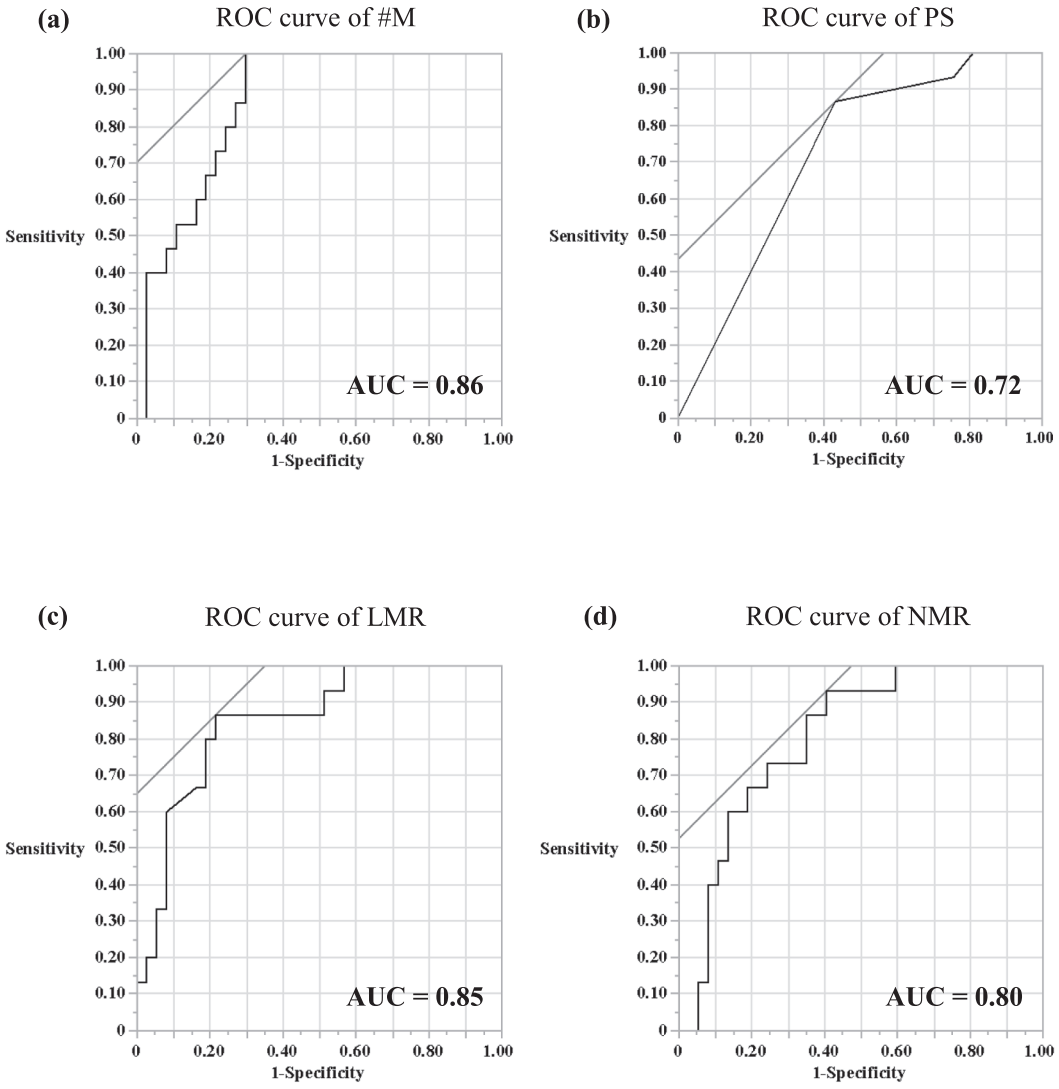

Fig. 1. ROC analysis for the predictive ability of promising parameters (a: #M, b: PS, c: LMR, d: NMR). ROC, receiver operating characteristic; AUC, area under the curve; #M, number of monocytes; PS, performance status; LMR, lymphocyte-monocyte ratio; NMR, neutrophil-monocyte ratio.

AUCs were 0.85 and 0.80 (Fig. 1c, 1d) and cutoff values were 2.5 and 16.1, respectively. #M and LMR were found to be the most valuable biomarkers.

3.5. Analysis of time of survival

Patients were dichotomized into subgroups based on the cutoff value of #M of 200 cells/μL and the time of survival for 1 year using the Kaplan–Meier method. A significantly shorter survival time was observed in the subgroup with #M ≤ 200 cells/μL ($p < 0.001$, log-rank test) (Fig. 2a). As for LMR, patients were dichotomized based on the cutoff value of LMR of 2.5, and the subgroup with LMR ≥ 2.5 presented a significantly shorter time of survival ($p < 0.001$, log-rank test) (Fig. 2b).

3.6. Three-week change in parameters after initiating anti-TB treatment

We selected patients with #M ≤ 200 cells/μL to compare the 3-week change in #M among the groups of death within and survival at 3 months to demonstrate that the longitudinal change in #M was related to successful treatment. #M in the group of survival at 3 months was significantly increased on days 8, 15, and 22, compared with that in the group of death within 3 months using paired *t*-test ($p = 0.002$, <0.001, and 0.004, respectively) (Supplementary Fig. 2a). The same trend was observed when analyzing the change in #L in patients with #M ≤ 200/μL on days 8, 15, and 22 ($p = 0.417$, 0.030, and 0.008, respectively) (Supplementary Fig. 2b). However, the 3-week change in LMR was not significant in either group (Supplementary Fig. 2c).

4. Discussion

To the best of our knowledge, this is the first study to demonstrate the predictive ability of monocytes in the prognosis of patients with MTB. This study revealed that biomarkers with monocytes, such as smaller #M, and higher LMR and NMR, were significantly associated with poor prognosis. LMR and NMR contained #M as the denominator, and #M had the highest AUC. Therefore, decreasing #M is the most important biomarker for poor prognosis.

The first explanation of the decreasing #M is bone marrow suppression secondary to severe inflammation, resulting in the inhibition of hematopoiesis. A previous report revealed that pancytopenia was found in relatively young patients with MTB and their prognosis was significantly poor [20]. Moreover, some studies have revealed thrombocytopenia and lymphocytopenia as risk factors for MTB [7,9,21,22]. In other diseases accompanied by severe inflammation, such as coronavirus

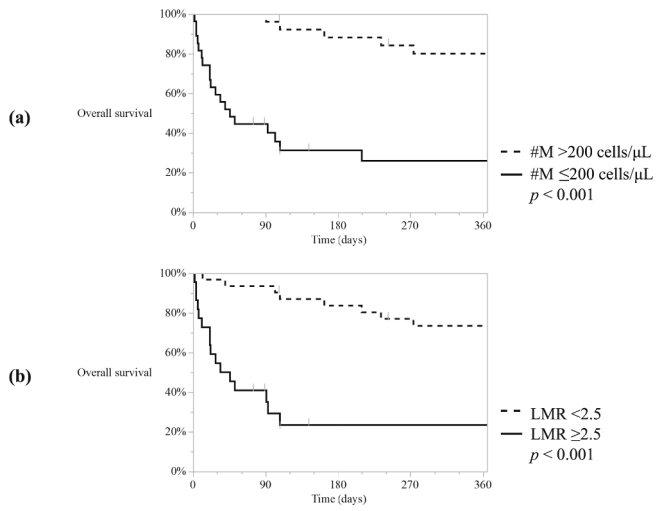

Fig. 2. Comparison of survival time (a: Kaplan–Meier curve of two subgroups divided by the cutoff value of #M ≤ 200 cells/μL. b: Kaplan–Meier curve of two subgroups divided by the cutoff value of LMR ≥ 2.5). #M, number of monocytes; LMR, lymphocyte-monocyte ratio.

disease and severe sepsis, including septic shock, monocytopenia was reported as a biomarker of prognosis [23,24]. In particular, a smaller #M was significantly associated with 28-day mortality compared with a larger #M in cases of severe sepsis [24]. These results were concordant with our results that #M ≤ 200 cells/μL was related to poor prognosis and monocytopenia improved with successful treatment. Thus, monocytopenia may be secondary to severe inflammation.

The second explanation is impaired hematopoiesis due to the bone marrow being occupied by granulomatous lesions. Previous studies reported that granulomatous lesions in the bone marrow were found in more than half of the patients with MTB [5,25], and participants in these studies had decreased numbers of leukocytes and platelets. These reports suggest that granulomatous lesions frequently accompany MTB and cause leukocytopenia. Therefore, it is reasonable to assume that granulomatous lesions in the bone marrow prevent hematopoiesis and result in monocytopenia.

The third possible explanation is the intensive recruitment of monocytes from the peripheral blood into the lung tissue for the formation of granulomatous lesions. Previous studies revealed that monocytes and lymphocytes play an important role in the immune response against *Mycobacterium tuberculosis* [12–14]. In this process, various cytokines, such as C-C motif chemokine 2 (CCL-2), are involved in the migration of monocytes to infectious sites [15–17]. In TB cases, higher concentrations of blood CCL-2 are associated with disease activity and severity [26–28]. In addition, murine data showed that the concentration of blood CCL-2 rapidly increased without treatment after infection, whereas it rapidly decreased according to the decreased amount of *Mycobacterium tuberculosis* by treatment commencement [29]. Moreover, higher concentrations of CCL-2 in the blood and an increasing #M in the bronchoalveolar lavage fluid were found in the acute phase of TB infection than in the convalescence phase [30,31]. These reports suggest that the influx of peripheral blood monocytes to infectious sites might be modulated depending on disease severity. MTB is a severe infectious disease with systemic dissemination of *Mycobacterium tuberculosis*, provoking a severe systemic immune response. Taken together, it is reasonable that the rapid migration of monocytes to many infectious sites resulted in a decrease in #M during the initial phase of infection.

In addition, our study revealed that rapidly increasing #M after treatment commencement was related to better prognosis in patients with #M ≤ 200 cells/μL, which was classified as a poor prognosis subgroup (Supplementary Fig. 2a). Regarding #L, the same trend was found (Supplementary Fig. 2b). This may be because successful treatment improved the severe inflammatory milieu, decreased the migration of monocytes and lymphocytes, and recovered the function of the bone marrow, which allowed the normalization of blood cells.

Many significant biomarkers in our study might not be specific for MTB but for severe inflammation. In an aging society, the older population comprises a major portion of patients with TB. In fact, approximately 83 % of the patients in our study were over 75 years of age. Previous reports have revealed that older patients with TB had atypical clinical presentations and tended to be at risk of diagnostic delay [32,33]. Delayed intervention results in a poor prognosis because of impaired physical condition and increased severity [11,34]. Although many biomarkers predicting poor prognoses, such as decreased leukocytes, higher BUN, impaired PS, and thrombocytopenia, were concordant with previous studies [8,9,11,20,21,35], these biomarkers might be related to the severity of inflammation rather than TB itself.

Our study has certain limitations. First, this was a retrospective study with a small sample size from a single institution. Furthermore, the imbalance in the background of the patients could not be removed, and some laboratory data were missing. Moreover, the accuracy of the clinical data was low because we collected them from medical records. In addition, a small number of patients were included in the analysis of the longitudinal change in #M, because many patients with #M ≤ 200 cells/μL died in 3 weeks. Therefore, a statistical comparison of #M on days 8, 15, and 22 between the two groups could not be conducted. Hence, further large-scale analyses are required.

5. Conclusion

#M is a useful biomarker to predict 3-month and 1-year prognoses. In addition, a rapid increase in #M predicts successful treatment in patients with MTB. Thus, #M at diagnosis and the longitudinal changes in monocytes serve as easy and useful biomarkers for predicting the prognosis of older patients with MTB.

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CRediT authorship contribution statement

Yusuke Shima: Supervision, Conceptualization, Data curation, Writing – original draft, Visualization, Investigation, Validation, Formal analysis, Methodology, Resources, Project administration. **Takahiro Masuda:** Data curation, Writing – review & editing, Resources, Investigation. **Nanako Miwa:** Data curation, Writing – review & editing, Investigation, Resources. **Yoko Kida:** Data curation, Writing – review & editing, Investigation, Validation, Formal analysis, Methodology. **Rikiya Koketsu:** Data curation, Writing – review & editing, Investigation, Formal analysis, Methodology, Resources. **Hiroshi Kamiryo:** Conceptualization, Data curation, Writing – review & editing, Visualization, Investigation, Formal analysis, Methodology, Supervision, Project administration. **Toshiyasu Sakurai:** Data curation, Writing – review & editing, Investigation, Resources. **Kimihide Tada:** Conceptualization, Data curation, Writing – review & editing, Visualization, Validation, Investigation, Funding acquisition, Project administration, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Shima received personal fees from AstraZeneca and Ono Pharmaceutical Co., Ltd. outside of the submitted work during the study period. The other authors declare that they have no conflicts of interest..

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Availability of data and materials

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

Ethics approval

This study was approved by the Kobe City Nishi-Kobe Medical Center Ethics Committee (approval number: 2022-25).

Consent to participate

This study was a retrospective analysis, and the requirement for informed consent to use the clinical information was waived; however, all participants were guaranteed opportunities to know and refuse to take part in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100437.

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