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Clinical relevance of ground glass opacity in 105 patients with miliary tuberculosis

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KEYWORDS
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Summary
Background: After the application of chest computed tomography (CT), ground glass opacity (GGO) was introduced as one of major accompanying findings of miliary tuberculosis (MT) in addition to miliary nodules. However, little is known about whether GGO is associated with the clinical manifestations and outcomes of MT. Therefore, the present study examined the clinical relevance of GGO in patients with MT.
Methods: Chest radiographs and CT scans of MT patients were retrospectively reviewed. Clinical manifestations and outcomes were compared in terms of the extent of GGO revealed by chest CT.
Results: Confirmed 105 MT patients were included. GGO was observed in 70 (67%) patients. MT patients with an extent of GGO >50% ($n = 21$) had symptoms of shorter duration, more frequent dyspnea, and more pronounced changes in the levels of acute phase reactants. Miliary nodules were less discernible on CT in those with an extent of GGO >50%. MT patients with an extent of GGO >50% were significantly associated with a longer hospital stay ($p = 0.02$) and with acute respiratory failure ($p < 0.001$) than those with an extent of GGO ≤50%. However, mortality among MT patients was not associated with the extent of GGO.
Conclusion: MT patients with an extent of GGO >50% had more rapidly progressive manifestations and a greater potential for delayed diagnosis and poorer prognosis. Nevertheless, mortality was not higher in confirmed MT patients with an extent of GGO >50% than in those with an extent of GGO ≤50%.

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Introduction

Miliary tuberculosis (MT) results from massive lymphohematogenous dissemination of *Mycobacterium tuberculosis* (MTB) during both primary and post-primary tuberculosis (TB) [1,2]. Despite the availability of effective treatments, mortality remains high. The clinical manifestations range from a rapidly progressive course to a slow and prolonged course with subtle clinical findings [2—4].

Findings of a classic miliary pattern on chest radiography provide an important clue when making a diagnosis of MT; however, initial chest radiographs often show a non-classic pattern or they can even be normal [5]. Thus, some patients with MT represent a diagnostic challenge. Chest computed tomography (CT) is more helpful and enables the early recognition of MT, even in patients with atypical or normal findings on chest radiography. Therefore, patients with suspected miliary nodules often undergo a chest CT. After the application of chest CT, several studies reported that ground glass opacity (GGO) was one of major accompanying findings of MT in addition to miliary nodules [6—9]. However, little is known about whether the extent of GGO is associated with the clinical manifestations and outcomes of these patients.

Therefore, the aim of the present study was to examine the clinical relevance of GGO in patients with MT. In addition, because a previous study noted that some MT patients had larger nodules in the lung apices than in the lung bases [6], we also identified these patients and described their clinical characteristics.

Materials and methods

Patients

The study was conducted at Kyungpook National University Hospital, a tertiary referral hospital in South Korea set in an area with an intermediate prevalence of active TB (149 cases per 100,000 population in 2011) [10]. All MT patients (aged $\geq$ 15 years) attending the hospital from April, 2001 to December, 2012 were retrospectively selected using ICD-10 code A190-A199. Those with available chest radiographs and CT scans were enrolled. Details regarding patient demographics, clinical manifestations, risk factors (e.g., human immunodeficiency virus (HIV) infection, malignancy, diabetes mellitus, immunosuppressive drug therapy, solid organ transplantation, end-stage renal disease, chronic liver disease, gastrectomy, alcoholism, or pregnancy), laboratory and microbiological data, histological data (if available), hospital course (initial admitting department, time from admission to the start of anti-tuberculous treatment, length of hospital stay, occurrence of respiratory failure, and the use of mechanical ventilation), and in-hospital mortality were obtained from the medical records. A final diagnosis was made in those patients suspected of having MT on the basis of clinical and radiographic examinations when a respiratory specimen or non-respiratory specimen (tissue other than lung or urine) was found to be culture-positive for MTB, or when there was histological evidence of chronic granulomatous inflammation and the tissue was positive for the acid fast bacilli (AFB) test or TB-polymerase chain reaction (PCR).

The study was approved by the Institutional Review Board of the Kyungpook National University Hospital.

Chest radiography and CT findings

Chest radiography and CT scans performed on admission were retrospectively reviewed by one board-certified radiologist and two board-certified pulmonologists who were blinded to the patient's clinical data. The initial chest radiographs and CT scans were obtained within 3 days of each other (median 0 day [interquartile range (IQR), 0-1]). Chest CT scans were performed with two multidetector CT scanners (LightSpeed, General Electric Medical Systems, Milwaukee, WI, USA; Aquilion 64, Toshiba Medical Systems, Otawara, Japan). Continuous axial images were obtained with 2.5 mm or 3 mm collimation from the lung apices to the bases at full inspiration. Images were reconstructed using a high spatial frequency (bone) algorithm and photographed in the mediastinal (window width, 350—240 H; level, 15—25 H) and lung windows (window width, 1500 H; level, −600 to −800 H).

The investigators independently assessed the pattern of the miliary lesions (classic miliary *vs.* non-classic miliary) on chest radiographs and the presence of miliary nodules (recognizable *vs.* non-recognizable) suggestive of MT on CT scans. A "classic" miliary pattern was defined as a collection of tiny discrete pulmonary opacities that were generally uniform in size and widespread in distribution, each of which measured $\leq$3 mm in diameter [2]. A "non-classic" miliary pattern was defined as the obscuring of background miliary nodules by diffuse GGO or the major findings characterized by an asymmetric nodular pattern, coalesced nodules, a mottled appearance, a snowstorm appearance, or air-space consolidation [2]. On chest CT, recognizable miliary nodules were defined when randomly distributed micro-nodules were well discernible on chest CT. By contrast, non-recognizable miliary nodules were defined when micro-nodules could not be clearly discernible on chest CT as the micro-nodules were superimposed on a background of other radiologic findings, such as GGO. However, patients in the latter group showed miliary nodules on short-term follow-up chest radiographs and/or CT scans taken after the other radiologic findings have resolved. The extent of GGO observed on chest CT was categorized as follows: 1) none; 2) less than one-quarter of the whole lung field; 3) less than one-half of the whole lung field but greater than one-quarter of the field; 4) greater than one-half of the whole lung field [7]. The zonal prominence (upper *vs.* even) of the nodules in size (when viewed along the cephalocaudal axis) was estimated by comparing the size of the miliary nodules at two levels of the chest CT scan: the upper end of the aortic arch and the lower end of the left atrium. Pre-existing active TB lesions, cavities, pleural effusion, nodules $\geq$4 mm in diameter, and mediastinal lymphadenopathy were comprehensively examined. A final decision on the findings was reached when the consensus of two observers was obtained (JL and JKL). A third observer (CHK) gave the final assessment if consensus could not be reached.

Statistical analysis

Statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, Ill). Each data set was tested for normality and equality of variances by means of the Shapiro–Wilk's test and Levene's test. Data with skewed distribution was analyzed after logarithmic transformation. Normal variables were expressed as the mean ± SD and analyzed using one-way ANOVA. For non-normal variables, medians were presented with IQR and Kruskal–Wallis test was used to compare differences among groups. Categorical variables were expressed as numbers and percentages and were analyzed using the χ^2 test or Fisher's exact test. A p value of 0.05 was considered significant.

Results

One hundred and thirty-two MT patients with available chest radiographs and CT scans were identified. Of these, clinically diagnosed ($n = 11$) and HIV-positive ($n = 10$) patients were excluded. Six patients who showed chronic granulomatous inflammation in the biopsy specimen without a positive AFB smear or TB-PCR result were also excluded. One hundred and five patients were microbiologically or histologically diagnosed with MT: 96 (91%) according to a positive MTB culture (sputum or bronchoscopic washing fluid [$n = 84$], urine [$n = 6$], pleural fluid [2], spine tissue [$n = 2$], transbronchial lung tissue [$n = 2$]) and 9 (9%) according to histological results (chronic granulomatous inflammation with positive AFB smear ($n = 4$) or TB-PCR ($n = 5$) results in tissue). Chest CT identified GGO in 70 (67%) patients. The extent of GGO was variable: none ($n = 35$), <25% ($n = 28$), 25–50% ($n = 21$), and >50% ($n = 21$). Whereas miliary nodules were uniformly distributed throughout both lungs, GGO was predominant in the lower lung zones.

Comparison of clinical features according to the extent of GGO on chest CT

There were no significant differences in the age distribution (according to a median of 64 years old), gender, or risk factors between groups showing a different extent of GGO on chest CT (Table 1). Patients with an extent of GGO >50% had symptoms of shorter duration prior to first presentation than those with an extent of GGO ≤50% ($p = 0.037$). There were no differences in constitutional symptoms and signs, including fever, between the groups. However, the number of patients reporting dyspnea increased proportionally with the extent of GGO ($p < 0.001$). Patients with an extent of GGO >50% reported dyspnea more frequently; indeed, these patients showed lower oxygen saturation on room air ($p < 0.001$). Although there were no differences in the white blood cell (WBC) count among the groups, C-reactive protein (CRP) increased and albumin levels decreased in patients with more extensive GGO ($p < 0.001$ and $p = 0.003$, respectively). There was no significant difference in the number of AFB smear-positive sputum samples among the groups.

Table 1 Comparison of clinical features according to the extent of ground glass opacity on chest CT in patients with miliary tuberculosis.

Clinical features	Total ($n = 105$)	Ground glass opacity				
		One ($n = 35$)	<25% ($n = 28$)	25–50% ($n = 21$)	>50% ($n = 21$)	*P* value
Age, years						
<65	53 (50)	23 (66)	11 (39)	8 (38)	11 (52)	0.113
≥65	52 (50)	12 (34)	17 (61)	13 (62)	10 (48)	
Male	50 (48)	17 (49)	14 (50)	9 (43)	10 (48)	0.966
Risk factors[a]	33 (31)	12 (34)	8 (29)	6 (29)	7 (33)	0.950
Symptom duration, day	30 (16–59)	30 (21–60)	30 (20–60)	30 (15–45)	19 (14–33)	0.037[b]
Weakness	92 (88)	29 (83)	27 (96)	17 (81)	19 (91)	0.268
Weight loss	76 (73)	26 (74)	22 (79)	11 (52)	17 (85)	0.108
Fever	80 (76)	28 (80)	19 (68)	16 (76)	17 (81)	0.656
Cough	60 (57)	21 (60)	14 (50)	11 (52)	14 (67)	0.643
Dyspnea	37 (35)	6 (17)	6 (21)	9 (43)	16 (76)	<0.001
WBC, cells/μL	6620 (5260–8760)	6530 (5390–7770)	6870 (5970–9120)	7230 (4203–8873)	6450 (4773–10475)	0.891
CRP, mg/dL	8.0 (3.3–12.2)	3.8 (1.0–6.7)	8.4 (3.1–14.5)	9.3 (5.9–17.6)	9.6 (6.1–14.8)	<0.001
Albumin, g/dL	2.9 ± 0.61	3.3 ± 0.58	3.0 ± 0.53	2.9 ± 0.54	2.7 ± 0.60	0.003
SpO_2 on room air, %	96 (90–98)	97 (96–98)	97 (93–98)	95 (93–97)	82 (68–91)	<0.001
Sputum AFB smear (+)[c]	27/82	8/26	4/22	7/16	8/18	0.510

Data are expressed as the number (%), mean ± SD, or median (IQR).
CT = computed tomography; WBC = white blood cell; CRP=C-reactive protein; SpO_2 = oxygen saturation by pulse oximetry; AFB = acid fast bacilli.
[a] Including malignancy, diabetes mellitus, immunosuppressive drug therapy, transplantation, end-stage renal disease, chronic liver disease, gastrectomy, alcoholism, or pregnancy.
[b] Becomes non-significant after correction for the number of comparisons.
[c] Positive number/performed number.

Comparison of radiological features according to the extent of GGO on chest CT

A classic miliary pattern was observed on chest radiographs in 54 (51%) of the 105 patients (Table 2). Seven (7%) patients who had normal findings on initial chest radiographs but who had a fever of unknown origin ($n = 3$), unexplained shortness of breath ($n = 2$), or developed new abnormal findings on follow-up chest radiographs ($n = 2$) were examined by a chest CT. However, a significant number of patients with an extent of GGO >50% (18/21, 86%; $p < 0.001$) did not show a classic miliary pattern on chest radiography. Chest CT identified miliary nodules in 91 (87%) of the 105 MT patients. Chest CT revealed findings suggestive of MT in all but one of the patients with an extent of GGO ≤50%, even though the chest radiographs showed a non-classic miliary pattern or were normal. One patient (with an extent of GGO of 25—50% and non-classic miliary findings on chest radiography) did not have miliary nodules on initial chest CT; however, miliary nodules were identified on follow-up chest radiographs and CT scans performed 7 days later and diagnosed with MT by a transbronchial lung biopsy. By contrast, 13 (62%) of the 21 patients with an extent of GGO > 50% were not suspected of having MT on initial chest CT. Thus, the number of inaccurate diagnoses based on the initial CT scan was significantly higher in this patient group ($p < 0.001$). A later diagnosis of MT was made in these patients (median delay before diagnosis was 4 days [IQR, 1—17]) when further evidence of TB (i.e., positive results for AFB smear, TB-PCR, or histology) and typical radiographic findings of MT with the resolution of GGO on subsequent chest radiographs and/or CT scans appeared. Pre-existing active lung lesions were observed in 52 (50%) patients. There were no significant differences in the incidence of the pre-existing active TB lesions, cavities, pleural effusion, and mediastinal lymphadenopathy between the groups.

The lung nodules in 76 (72%) patients were approximately the same size and shape; however, in 29 (28%) patients, the apical nodules were larger than the basal nodules (Fig.1). The number of patients with larger nodules in the upper lung field was significantly different between the four groups ($p = 0.002$) (Table 2). The proportion of patients with upper-prominent or evenly-sized nodules was similar in the non-GGO group whereas the proportion of patients with evenly-sized nodules was higher in the GGO groups. Most of the nodules measured 1—3 mm in diameter; however, nodules ≥4 mm in diameter, irrespective of the extent of GGO, were present in eight (8%) patients.

Comparison of clinical outcomes according to the extent of GGO on chest CT

Although the mean time from admission to the start of anti-tuberculosis treatment and the number of patients with delay of greater than 3 days to diagnosis increased proportionally with the extent of GGO, the differences were not statistically significant. Acute respiratory failure occurred significantly more often in the group with an extent of GGO >50% ($p < 0.001$) (Table 3). Seven patients in this group suffered acute respiratory failure that manifested as acute respiratory distress syndrome (ARDS). No cases of ARDS were identified in the other groups. The length of hospital stay for the surviving patients was significantly longer in the group with an extent of GGO >50% ($p = 0.024$). However, there was no difference in in-hospital mortality (10% overall) between the groups.

Comparison of clinical and radiological findings according to the prominence of nodules on chest CT

Patients with upper-prominent nodules experienced symptoms of longer duration than those without (54 ± 43 *vs.* 36 ± 32 days, respectively; $p = 0.018$). They also showed higher oxygen saturation on room air (94 ± 5.6 *vs.* 89 ± 15.0%, respectively; $p = 0.047$). There were no significant differences in terms of age distribution, gender, risk factors, frequency of clinical signs and symptoms, WBC, or albumin levels between the upper-prominent and non-prominent groups. The patients with upper-prominent nodules showed a significantly lower incidence of GGO on CT than those without (12/29 [41%] *vs.* 58/76 [76%], respectively; $p = 0.001$) (Table 2). All eight patients with nodules measuring ≥4 mm in diameter belonged to the group with upper-prominent nodules (28 *vs.* 0%, $p < 0.001$). However, there was no difference in clinical outcomes including mortality between both groups.

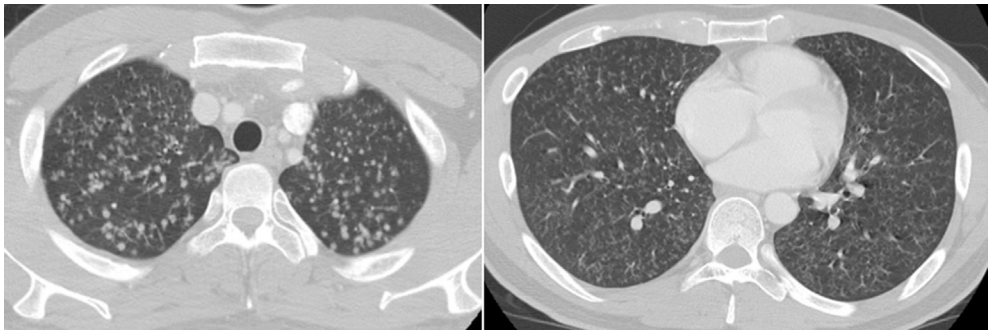

Figure 1 Chest CT in a 27-year-old man. CT scans at two levels show numerous small nodules 1—5 mm in diameter. The nodules in the upper lobes (left) are larger than those in the lower lobes (right).

Table 2 Comparison of radiologic features according to the extent of ground glass opacity on chest CT in patients with miliary tuberculosis.

Radiologic features	Total (n = 1 05)	Ground glass opacity				
		None (n = 35)	<25% (n = 28)	25–50% (n = 21)	>50% (n = 21)	P value
Chest X-ray pattern						
Classic miliary	54 (51)	21 (60)	15 (54)	15 (71)	3 (14)	<0.001
Non-classic miliary	44 (42)	10 (29)	10 (36)	6 (29)	18 (86)	
Negative	7 (7)	4 (11)	3 (11)	0 (0)	0 (0)	
Chest CT findings						
Miliary nodules						
Recognizable	91 (87)	35 (100)	28 (100)	20 (95)	8 (38)	<0.001
Non-recognizable	14 (13)	0 (0)	0 (0)	1 (5)	13 (62)	
Preexisting active TB lesions	52 (50)	17 (49)	11 (40)	13 (62)	11 (52)	0.200
Cavity	24 (23)	8 (23)	8 (29)	4 (19)	4 (19)	0.875
Pleural effusion	32 (31)	7 (20)	9 (32)	7 (33)	9 (43)	0.327
Mediastinal lymphadenopathy	31 (30)	11 (31)	4 (14)	8 (38)	8 (38)	0.177
Prominence of nodules in size						
Upper	29 (28)	17 (49)	5 (18)	6 (29)	1 (5)	0.002
Even	76 (72)	18 (51)	23 (82)	15 (71)	20 (95)	
Nodules ≥ 4 mm in size	8 (8)	5 (14)	1 (4)	2 (10)	0 (0)	0.220

Data are expressed as the number (%).
CT = computed tomography; TB = tuberculosis.

Discussion

The present study classified MT according to the extent of GGO. The results showed the following: 1) MT patients with an extent of GGO >50% experienced symptoms for a shorter time prior to admission and were more likely to suffer from dyspnea than those with an extent of GGO ≤50%; 2) CRP levels increased and albumin levels decreased in line with the extent of GGO; 3) chest CT was suggestive of MT in 37 (73%) of 51 patients showing either a non-classic miliary pattern or normal findings on chest radiography; however, miliary nodules suggestive of MT were significantly more difficult to visualize on chest CT in patients with an extent of GGO > 50%; 4) upper-prominent miliary nodules were observed in 28% of MT patients, and occurred more frequently in patients without GGO than in those with GGO; and 5) there was a significant increase in the length of hospital stay and in the incidence of acute respiratory failure in MT patients with an extent of GGO > 50%.

The clinical manifestations of MT comprise mainly non-specific constitutional symptoms and signs, the most notable being a persistent low-grade fever. Respiratory symptoms are less common. In the present study, the frequency of particular signs and symptoms was not significantly different from that reported in previous studies [4,11–16]. However, dyspnea (supported by the finding of low oxygen saturation on room air) was one of major symptoms in patients with an extent of GGO > 50%. The shorter duration of symptoms prior to admission in these patients may be due to the development of dyspnea, which can limit daily activities and is more distressing than other symptoms.

A miliary pattern on the chest radiographs is the hall mark of MT and is often the first clue to diagnosis. However, a classic miliary pattern is not evident on chest radiographs in up to 50% of patients [3,17,18]. The present study showed a non-classic miliary pattern in 49% of MT patients. The non-classic miliary patterns in these cases may be attributed to pre-existing lung lesions and GGO. CT is superior to chest radiography for evaluating chest-related diseases. It can identify tiny nodules in even cases with normal findings on chest radiography and define the anatomic distribution of micro-nodules within the lungs [7,8]; this is helpful for diagnosing MT characterized by randomly distributed tiny nodules. Ninety-one (87%) patients in the present study were suspected of having MT based on chest CT (Table 2). Thirteen (93%) of the remaining 14 patients, of whom miliary nodules were not discernible on chest CT, had an extent of GGO > 50%. In contrast to chest radiography, pre-existing lung lesions including cavity or consolidation on chest CT may be helpful for the suspicion of MT in conjunction with miliary nodules. However, extensive GGO makes the recognition of miliary nodules difficult. Therefore, MT patients who were not suspected of having MT even after the application of chest CT are likely to be attributed to extensive GGO.

Two previous studies with 14 and 25 MT patients reported the incidence of GGO as 64% and 92%, respectively [7,9]. The present study showed that the incidence of GGO in MT patients was 67%. GGO was not uniformly distributed and it was transient, unlike miliary nodules uniformly distributed and persisted several weeks even after treatment. Thus, GGO is considered to represent a transient exudative change [8]. We found that GGO was predominant in the lower portion of the lung, reflecting the perfusion gradient. Patients with an extent of GGO >50% had more acute symptoms and showed more profound changes in the levels of acute phase reactants such as CRP and albumin. Some patients with extensive GGO developed ARDS. Thus, extensive GGO in patients with MT may indicate a more rapidly progressive form of MT. Differences in the extent of

Table 3 Comparison of clinical outcomes according to the extent of ground glass opacity on chest CT in patients with miliary tuberculosis.

Clinical outcomes	Total (n = 105)	Ground glass opacity				
		None (n = 35)	<25% (n = 28)	25–50% (n = 21)	>50% (n = 21)	P value
Time to anti-TB treatment, day	1 (0–3)	1 (0–3)	1 (0–3)	1 (1–4)	2 (1–5)	0.653
Delay > 3 days to diagnosis	23 (22)	5 (14)	6 (21)	5 (24)	7 (33)	0.404
Acute respiratory failure	11 (10)	1 (3)	0 (0)	3 (14)	7 (33)	<0.001
Hospital length of stay in survivor, day	15 (9–24)	13 (7–27)	15 (7–21)	15 (11–22)	22 (17–39)	0.024[a]
Mortality	11 (10)	2 (6)	3 (11)	3 (14)	3 (14)	0.670

Data are presented as the number (%) or median (IQR).
CT = computed tomography; TB = tuberculosis.
[a] Becomes non-significant after correction for the number of comparisons.

GGO in these patients might be associated with inter-individual differences in the inflammatory response to disseminated tubercle bacilli. This type of response may depend on interplay between mycobacterial virulence and host immunity [19,20]. However, future study needs to be done to fully explain why some MT patients develop extensive GGO.

The present study confirmed that patients with extensive GGO suffer more frequent episodes of dyspnea and ARDS [7,8,21,22]. The length of hospital stay was significantly greater for survivors with an extent of GGO > 50%. In addition, it should be noted that 7 patients with delayed anti-TB treatment and an extent of GGO >50% were initially admitted in pulmonary department (Table 3). These findings suggest that early diagnosis of MT in patients with extensive GGO may be difficult in even experienced clinicians who are familiar with MT. Thus, clinicians should have a high index of suspicion for MT when patients present with extreme GGO or unexplained ARDS.

The present study examined the prominence of miliary nodules in the cephalocaudal axis. Upper-prominent nodules were noted in previous studies [7,23]. In some patients with MT, the disease can be protracted rather than rapidly progressive. [2,3] Gurney et al. [24] described that, in cases of advanced MT, nodules at the lung apex are larger than those at the base. The oxygen-rich environment in the upper lung provides more favorable conditions for the growth of MTB [25]. Thus, upper-prominent nodules may suggest more advanced or protracted form rather than rapidly progressive form with extensive GGO. To the best of our knowledge, the incidence of upper-prominent nodules in a large population of MT patients has not been examined since the introduction of effective anti-TB drugs. The present study identified upper-prominent nodules in 28% of MT cases. These patients suffered symptoms of significantly longer duration than those without, although the mortality rate was the same for both groups (10%). In addition, eight (28%) of these patients with upper-prominent nodules had nodules ≥4 mm in diameter. Thus, this form of MT should be considered in the differential diagnosis of pneumoconiosis or hematogenous miliary metastasis showing variable sized nodules. Fever and the presence of larger nodules in the upper lungs may help to distinguish MT from other diseases characterized by lung nodules of variable size.

The present study has several limitations. First, the cohort included microbiologically- or pathologically-confirmed cases of MT. Many patients with MT are clinically diagnosed. In addition, patients with extreme GGO may have died from acute respiratory failure prior to diagnosis. Thus, we may have underestimated the overall incidence and mortality rate, particularly in patients with an extent of GGO >50%. Second, we did not investigate the long-term effect of GGO on patient outcomes. Third, the present study included patients for whom chest radiographs and CT scans were performed concurrently. However, this does not mean that CT should be routinely recommended for all patients suspected of having MT, unless the results of chest radiography are atypical. Finally, certain multiplicity problems may have resulted from the comparison of multiple parameters. However, all the significant findings remained after correction for the number of comparisons apart from symptom duration and hospital stay in survivors. The corresponding variables need to be tested in further confirmatory studies.

In conclusion, the present study systematically documents the clinical relevance of GGO in patients with MT and additional information with respect to upper-prominent nodules in the cephalocaudal axis. Patients with an extent of GGO >50% had a more serious presentation and a greater potential for delayed diagnosis and a poorer prognosis. Nevertheless, the mortality was not greater in confirmed MT patients with an extent of GGO >50% than in those with an extent of GGO ≤50%.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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