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Body composition changes successfully classify prognosis in patients with *mycobacterium avium complex* lung disease

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SUMMARY

Objectives: Loss of body weight, a manifestation of cachexia, is frequently found in patients with *Mycobacterium avium complex* lung disease (MAC-LD) and known as a prognostic determinant. However, the involvement of body composition changes in the prognosis of patients with MAC-LD remains unclear.
Methods: The cross-sectional-area of the erector spinea muscle (ESM_{CSA}) and mean attenuation of the erector spinae muscles (ESM_{MA}) in patients with MAC-LD, as determined by computed tomography imaging, were measured in two independent cohorts (137 and 111 patients, respectively).
Results: Patients with MAC-LD showed significantly smaller ESM_{CSA} together with lower body mass index (BMI), but no difference in ESM_{MA} in both cohorts compared with controls. Smaller ESM_{CSA}, body mass index decline, and decreased ESM_{MA} were associated with worse survival in the patients. Among them, decreased ESM_{MA} showed prognostic significance in the multivariate analyses. Importantly, assessment by ESM_{MA} together with BMI successfully divided the patients into three groups with distinct prognoses.
Conclusion: Changes in body composition, especially decreased ESM_{MA}, had prognostic significance in patients with MAC-LD. Additionally, combined assessment of ESM_{MA} and BMI accurately predicted the prognosis of MAC-LD, which may be a helpful tool for disease management.

Introduction

Non-tuberculous mycobacteria (NTM) pulmonary disease can cause chronic pulmonary infection and is becoming increasingly recognised as an emerging global health problem.[1] Among the species, *Mycobacterium avium complex* (MAC) are the most common pulmonary NTM pathogens in almost all regions of the world. The prevalence of NTM is gradually increasing worldwide and is significantly associated with morbidity, mortality, and health care costs.[2–4] Patients with MAC lung disease (MAC-LD) often complain of weight loss associated with a slender stature, termed pulmonary cachexia. These physiological body composition changes are reportedly associated with disease pathogenesis, and lower BMI or weight loss has been reported as prognostic determinants in patients with MAC-LD.[1,5–10]

Skeletal muscle wasting, derived from imbalance between protein synthesis and protein degradation, is a cardinal feature of cachexia. Cachexia, a hyper-catabolic state, is characterised by skeletal muscle loss with or without loss of fat mass accompanied by underlying illness and is partly mediated by the chronic inflammatory response.[11,12] Importantly, cachexia-induced skeletal muscle loss results in decreased muscle strength and reduced quality of life, leading to lower activity and increased exercise intolerance. Cachexia is considered an independent prognosis determinant in several diseases including cancer,[13,14] COPD,[15,16] and congestive heart failure.[17] Therefore, elucidating the mechanisms and developing effective treatments for this condition are of priority.

Several methods are currently used for the assessment of skeletal muscle loss such as body weight measurement, the body mass index (BMI), and dual-energy X-ray absorption.[15] Computed tomography (CT) and magnetic resonance imaging (MRI) are also clinically used to this end. In the analyses of patients with multi-organ cancer, the lumbar skeletal muscle area and its attenuation at the third lumbar vertebra (L3) was associated with poor

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survival regardless of BMI.[13] Similarly, quantitative CT measurements of the erector spinae muscles (ESM), a major antigravity muscle group, have shown prognostic value in patients with COPD[18] and interstitial pneumonias.[19]

As loss of lean body mass is frequently found in patients with MAC-LD, we hypothesised that body composition changes might be involved in the prognosis of MAC-LD. Thus, the present study sought to investigate morphological changes in skeletal muscle and their clinical implications by quantitative measuring the ESM in patients with MAC-LD.

Methods

Subjects

This retrospective study was conducted with two cohorts of patients with MAC-LD available for CT at the time of diagnosis. A cohort of 209 consecutive patients with MAC-LD admitted to Seirei-Mikatahara Hospital and a cohort of 137 patients with MAC-LD hospitalised at Tenryu hospital were enrolled in this study. Of the 331 patients, 69 whose observation period was shorter than 6 months and 14 patients not available for BMI measurements values were excluded. Thus, this study enrolled 137 patients with MAC-LD from the Mikatahara cohort and 111 patients with MAC-LD from the Tenryu cohort. None of the patient had advanced malignancies at the time of MAC-LD diagnosis. Diagnosis of MAC was based on the 2007 American Thoracic Society diagnostic criteria.[1] This study also included 58 age- and sex matched subjects (25 men and 33 women; mean age, 71.5 years) who visited Hamamatsu University Hospital for health check-ups as a control group. None of the control subjects had lung cancer or mycobacterium tuberculosis, as assessed by chest radiography.

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (17–196) and carried out in accordance with the approved guideline. The need for patient approval and/or informed consent was waived due to the retrospective nature of the study.

CT image analysis

Electronically stored CT-images were used to assess muscle mass. All CT-images were taken at the time of MAC-LD diagnosis during routine clinical practice. Chest CT was performed in the supine position at full inspiration breath-hold, at 120 kVp and approximately 200 mA. Using a modified method, as described in a previous article,[13,18–20] chest CT images were reconstructed in a mediastinal setting (reconstruction kernel FC13). Single slice axial CT-images (contrast unenhanced condition; 5-mm thickness and 5-mm interval) acquired at the lower margin of the 12th thoracic vertebra (Th12) were selected to measure the ESM cross-sectional area (ESM_{CSA}). After imaging, the ESMs were identified and manually shaded; ESM_{CSA} quantification was based on Hounsfield unit (HU) thresholds (−29 to +150) and the mean ESM muscle attenuation (ESM_{MA}) (HU) levels were assessed as previously described.[13,19] All CT analyses were independently performed by trained individuals (DA and YS) blinded to the patients' survival statuses and then averaged. Images were analysed using SYNAPSE VINCENT version 3 (FUJIFILM Medical Systems, Tokyo, Japan).

Data collection

Clinical data were obtained from the patients' medical records. Clinical and laboratory findings obtained at the time of diagnoses were recorded.

Statistical analysis

Discrete variables are expressed as totals (percentages), and continuous variables are expressed as median [interquartile range]. The Mann-Whitney test was used to compare continuous variables, and the Kruskal–Wallis test and post hoc analyses were used for multiple comparisons. Fisher's exact tests for independence were used to compare categorical variables. Correlations were analysed using the Spearman's rank correlation coefficient. Overall survival time was measured from the date of MAC-LD diagnosis. To examine the impact of body composition changes on prognosis, two distinct cohorts (the Mikatahara cohort as a discovery cohort and the Tenryu cohort as a validation cohort) were evaluated. The optimal cut-off values of the ESM_{CSA}, ESM_{MA}, and BMI in the Mikatahara cohort were applied to evaluate the Tenryu cohort and the combined cohort data. Cumulative survival probabilities were estimated using the Kaplan–Meier method with the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model with the combined cohort subjects to predict all-cause mortality. Among the statistically significant covariates in the univariate analyses, several covariates were excluded because of potential confounders and statistical limitations. Statistical analyses were performed using GraphPad Prism Version 6 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics (Ver. 23, IBM Corporation, Armonk, NY, USA). All analyses were two-tailed and p values less than 0.05 were considered significant.

Results

Clinical characteristics

The clinical characteristics of the 137 patients with MAC-LD in the Mikatahara cohort and 111 patients in the Tenryu cohort are summarised in Table 1. The Mikatahara cohort consisted of slightly older individuals than did the Tenryu cohort. There were no obvious differences in sex, observation period, mortality, and infected species between the two cohorts. Most patients had lower BMI compared to the controls. Radiographic analyses showed that 70–80% of patients had a nodular-bronchiectasis pattern, while fibro-cavitary disease was found in 20–30% of the patients. Regarding comorbidities, pulmonary diseases, such as sequelae of pulmonary tuberculosis, chronic obstructive pulmonary disease, interstitial lung disease, and pulmonary aspergillosis were present in approximately 10% of the patients. Combined lung cancer was frequently observed in the Mikatahara cohort. During the observation period, more than half of the patients were treated with guideline-based therapy (rifampicin, clarithromycin, and ethambutol), and the proportions of treated patients tended to be higher in the Mikatahara cohort.

Measurements of ESM_{CSA} and ESM_{MA}

The distributions of ESM_{CSA}, ESM_{MA}, and BMI in the Mikatahara cohort are presented in Fig. 1. The ESM_{CSA} of the patients with MAC-LD in the Mikatahara cohort was significantly smaller than that of the control subjects (Mikatahara, 25.2 [21.8–29.7] cm^2; controls, 33.7 [25.9–40.9] cm^2; $p < 0.0001$). Meanwhile, no difference was found in ESM_{MA} (Mikatahara, 40.3 [34.9–45.1] HU; controls, 39.7 [35.9–44.1] HU). However, the proportion of subjects with ESM_{MA} less than 20 HU was larger in patients with MAC-LD than in controls. The BMI was significantly lower in the Mikatahara cohort than in controls (Mikatahara, 18.7 [16.9–21.0] kg/m^2; controls, 22.8 [20.5–25.6] kg/m^2; control $p < 0.0001$).

In the Tenryu cohort, similar to the Mikatahara cohort, the patients with MAC-LD had significantly smaller ESM_{CSA} than did

Table 1
Clinical characteristics of patients with mycobacterium avium complex lung disease.

	Mikatahara Cohort ($n = 137$)	Tenryu Cohort ($n = 111$)	p-value
Age, year	73 [65–78]*	76 [67–82]	0.071
Sex, men/women, no. (%)	58 (42.3%) /79 (57.7%)	40 (36.0%) /71 (64.0%)	0.361
Observation period, mo	55.0 [39.0–83.0]	69.0 [32.0–91.0]	0.516
Mortality, no. (%)	30 (21.9%)	14 (12.6%)	0.067
Microbiological findings, no. (%)			
Avium/intracellulare	63 (46.0%) /74 (54.0%)	50 (45.0%) /61 (55.0%)	0.899
Sputum smear (−, ±, 1+, 2+, 3+)	59 (43.1%) /42 (30.7%) /12 (8.8%) / 21 (15.3%) / 3 (2.2%)	47 (42.7%) /16 (14.5%) /10 (9.1%) /16 (14.5%) /21 (19.1%)	<0.001
Radiographic pattern, no. (%)			
NB/FC	100 (73.0%) /37 (27.0%)	89 (80.2%) /22 (19.8%)	0.230
Comorbidity, no. (%)			
COPD	14 (10.2%)	12 (10.8%)	1.000
Interstitial lung disease	13 (9.5%)	7 (6.3%)	0.463
Lung cancer	11 (8.0%)	2 (1.8%)	0.042
Pulmonary Aspergillosis	14 (10.2%)	6 (5.4%)	0.241
Sequelae of PTB	16 (11.7%)	8 (7.2%)	0.284
Diabetes mellitus	11 (8.0%)	12 (10.8%)	0.512
Laboratory findings at diagnosis			
WBC, /μl	5950 [4920–7040]	5300 [4300–6900]	0.015
Hb, g/dl	12.5 [11.2 −13.7]	12.3 [11.5–13.4]	0.687
CRP, mg/dl	0.3 [0.1–1.0]	0.2 [0–0.9]	0.071
TP, g/dl	7.3 [6.9–7.6]	7.2 [6.9–7.6]	0.619
Alb, g/dl	3.9 [3.6–4.1]	4.0 [3.5–4.3]	0.144
LDH, IU/l	192 [170–215]	194 [172–222]	0.466
Treatment, no. (%)			
CAM+RFP+EB	85 (66.4%)	58 (52.3%)	0.034
Surgery	5 (3.6%)	1 (0.9%)	0.229

BMI; body mass index, ESM_{CSA}; cross-sectional area of elector spine muscles, ESM_{MA}; muscle attenuation of elector spine muscles, NB; nodular/bronchiectatic, FC; fibrocavitary, WBC; white blood cell, Hb; hemoglobin, CRP; C-reactive protein, TP; total protein, Alb; alubumin, LDH; lactate dehydrogenase, CAM; clarithromycin, RFP; rifampicin, EB; ethambutol, COPD; chronic obstructive pulmonary disease, PTB; pulmonary tuberculosis. *Median [interquartile range].

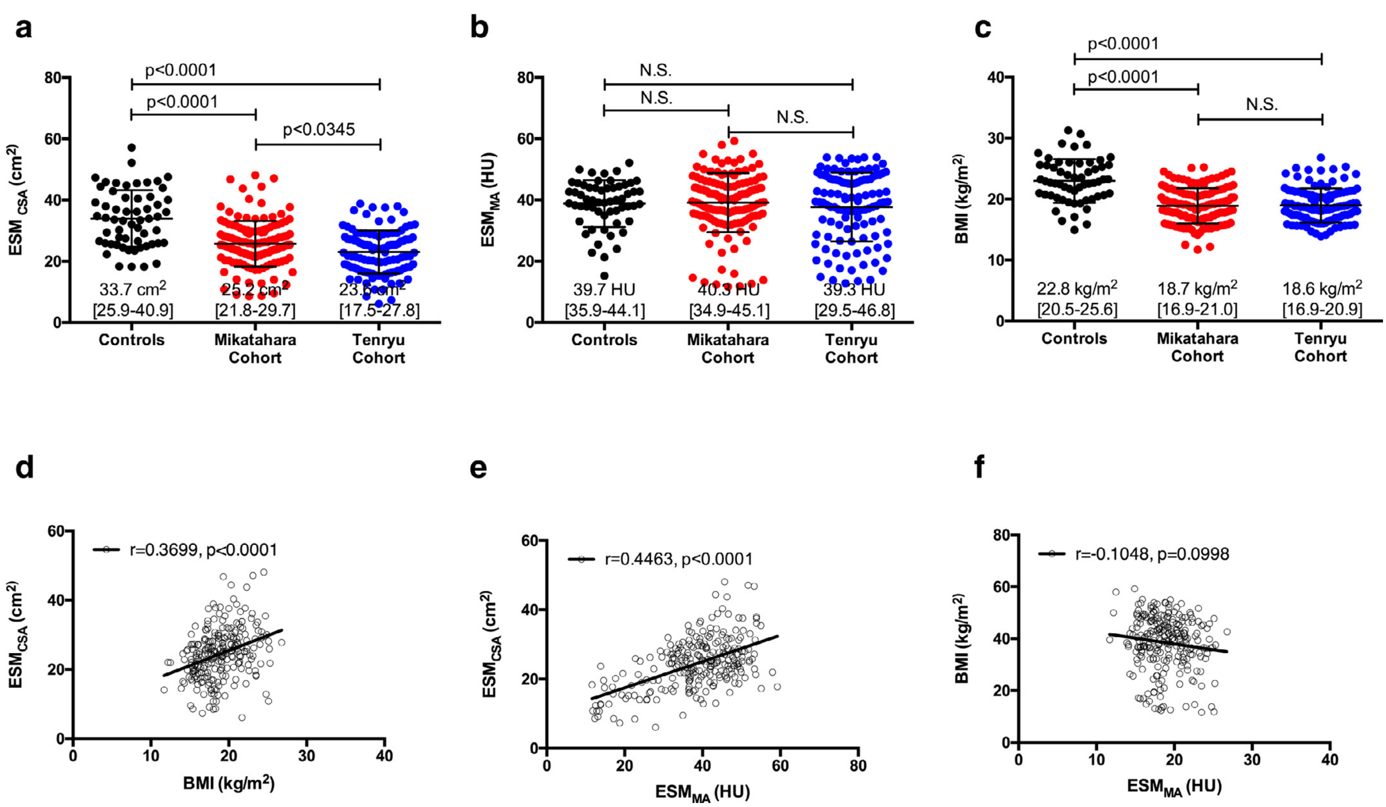

Fig. 1. *Prevalence of changes in body composition in patients with MAC-LD.*
The distributions of ESM_{CSA} (**a**), ESM_{MA} (**b**), and BMI (**c**) in patients with MAC-LD and controls. Correlations between ESM_{CSA}, ESM_{MA}, and BMI in patients with MAC-LD and controls (**d–f**).
MAC-LD: *Mycobacterium avium complex* lung disease, ESM: erector spinae muscles, CSA: cross-sectional area, MA: muscle attenuation, BMI: body mass index.

Table 2
Correlations analyses of ESM_{CSA} and ESM_{MA}.

Variables	ESM_{CSA}		ESM_{MA}	
	r	P-value	r	P-value
Age (year)	−0.4170	<0.0001	−0.4391	<0.0001
BMI (kg/m^2)	0.3699	<0.0001	−0.1048	0.0998
ESM_{CSA} (cm^2)	–	–	0.4463	<0.0001
ESM_{MA} (HU)	0.4463	<0.0001	–	–
WBC, /μl	0.0885	0.1667	0.0860	0.1787
Hb, g/dl	0.3035	<0.0001	0.0765	0.2316
CRP, mg/dl	−0.0962	0.1332	−0.1487	0.0199
TP, g/dl	−0.0043	0.9468	0.0764	0.2347
Alb, g/dl	0.1763	0.0061	0.1209	0.0608
LDH, IU/l	−0.11020	0.1113	−0.0794	0.2156

BMI; body mass index, WBC; white blood cell, Hb; hemoglobin, CRP; C-reactive protein, TP; total protein, Alb; albumin, LDH; lactate dehydrogenase.

the controls (Tenryu, 23.6 [17.5–27.8] cm^2; controls, 33.7 [25.9–40.9] cm^2; $p < 0.0001$), while ESM_{MA} did not differ between patients and controls (Tenryu, 39.3 [29.5–46.8] HU; controls, 39.7 [35.9–44.1] HU). Similar to the Mikatahara cohort, however, the proportion of subjects with ESM_{MA} less than 20 HU was much larger in patients with MAC-LD than in controls. The BMI was significantly lower in the Tenryu cohort than in controls (Tenryu, 18.6 [16.9–20.9] kg/m^2; controls, 22.8 [20.5–25.6] kg/m^2; $p < 0.0001$).

Between the two cohorts, the ESM_{CSA} value was slightly lower in the Tenryu cohort than in the Mikatahara cohort ($p = 0.0345$), while the ESM_{MA} and BMI values did not differ significantly between the two cohorts.

Correlations of ESM_{CSA} and ESM_{MA}

Correlations between ESM_{CSA}, ESM_{MA}, BMI, and clinical parameters are shown in Fig. 1d–f, and Table 2. Significant correlations were found between ESM_{CSA} vs. BMI and ESM_{CSA} vs. ESM_{MA} in patients with MAC-LD in the combined two cohorts ($r = 0.3699$, $p < 0.0001$ and $r = 0.4463$, $p < 0.0001$, respectively). Meanwhile, ESM_{MA} did not correlate with BMI ($r = -0.1048$, p - 0.0998). These results were consistent when fibro-cavitary and nodular-bronchientasis disease were analyzed separately (data not shown). In patients with MAC-LD, age was well correlated with the ESM_{CSA} and negatively correlated with $ESM_{MA.}$ However, the ESM_{CSA} and ESM_{MA} showed only weak or no correlations with C-reactive protein, serum total protein, or serum albumin levels.

Prognostic value of ESM_{CSA}, ESM_{MA}, and BMI in patients with MAC-LD

During follow up (Mikatahara, 55.0 [39.0–83.0] months; Tenryu, 69.0 [32.0–69.0] months, respectively), 30 patients in the Mikatahara cohort and 14 in the Tenryu cohort died. The causes of death in the Mikatahara cohort included progression of MAC-LD ($n = 13$), interstitial lung disease ($n = 4$), lung cancer ($n = 4$), other malignancy diseases ($n = 4$), bacterial pneumonia ($n = 2$), and others ($n = 3$). The causes of death in the Tenryu cohort included progression of MAC-LD ($n = 8$), interstitial lung disease ($n = 1$), lung cancer ($n = 1$), COPD ($n = 1$), and unknown causes ($n = 3$). To evaluate the potential values of ESM_{CSA}, ESM_{MA}, and BMI for predicting the prognosis of MAC-LD, receiver operation characteristic (ROC) analyses were performed in the Mikatahara cohort as a derivation cohort. First, due to the difference in body composition between men and women, we set separate cut-off values for the ESM_{CSA} for the two sexes. In the Mikatahara cohort, with optimal ESM_{CSA} cut-off values of 29.6 cm^2 in men and 24.5 cm^2 in women, the sensitivity and specificity were 73.3% and 46.7%, respectively (Supplemental Table 1). In the Tenryu cohort, the sensitivity and specificity were 85.7% and 35.1%, respectively. Optimal cut-off vales of ESM_{MA} and BMI were defined as 38.0 (HU) and 18,5 (kg/m^2), respectively. In the Mikatahara cohort, the sensitivity and specificity of ESM_{MA} were 60.0% and 65.4%, respectively, while those of the BMI were 70.0% and 58.9%, respectively. In the Tenryu cohort, the sensitivity and specificity of ESM_{MA} were 71.4% and 58.8%, respectively, while those of the BMI were 71.4% and 54.6%, respectively.

We next examined the prognosis of patients with MAC-LD using the Kaplan–Meier method and the log-rank test with the obtained cut-off values (Fig. 2). In the Mikatahara cohort, smaller ESM_{CSA}, decreased ESM_{MA}, and BMI decline were significantly associated with worse prognosis ($p = 0.0424$, $p = 0.0368$, $p = 0.0052$, respectively; Fig. 2a–c). Further, we applied these cut-off values to the Tenryu cohort and the combined cohorts. In the Tenryu cohort, patients with small ESM_{CSA} and decreased ESM_{MA}, but not with BMI decline, showed worse survival ($p = 0.0439$, $p = 0.0104$, and $p = 0.0604$ respectively; Fig. 2d–f). In the combined cohort, small ESM_{CSA}, decreased ESM_{MA}, and BMI decline were significantly associated with poor prognosis ($p = 0.0186$, $p = 0.0012$, and $p = 0.0006$, respectively; Fig. 2g–i).

Univariate and multivariate analyses of ESM_{CSA} and ESM_{MA} for mortality

Next, we assessed the prognostic implications of body composition changes by Cox proportion-hazard regression analyses in all patients. As shown in Table 3, univariate analyses revealed that older age, male sex, and factors related to muscle wasting, such as smaller ESM_{CSA} ($p = 0.002$), decreased ESM_{MA} ($p = 0.002$), and BMI decline ($p = 0.002$) were significantly associated with mortality. When applied to continuous valuables, the ESM_{MA} and BMI values were also significant. Give that age and sex may affect body mass, we performed adjusted multivariate analyses with age and sex. In the multivariate analyses, both ESM_{MA} and male sex were independently associated with mortality in patients with MAC-LD.

Clinical utility of composite parameters of body composition changes for predicting prognosis

For predicting the prognosis of patients with MAC-LD, sole body composition-related parameter showed relatively higher negative predictive values. Thus, we further assessed the prognostic utility of combinations of two out of the ESM_{CSA}, ESM_{MA}, or BMI based on the optimal cut-off values obtained above. Patients were categorised into three groups; 1) patients in whom both values were above the cut-off, 2) patients in whom both values were below the cut-off, and 3) the remaining patients. Patients with “low ESM_{CSA} and low ESM_{MA}”, “low ESM_{MA} and low BMI”, and “low ESM_{CSA} and low BMI” showed the worst prognosis (Fig. 3a–c). Particularly, the combination of ESM_{MA} and BMI showed the best prognostic separation ability based on the log-rank test (mortality rate 5.2%, 17.8%, 35.8%, respectively, $p < 0.01$; Fig. 3b).

Discussion

The present study assessed body composition changes by measuring ESM_{CSA} and ESM_{MA} in patients with MAC-LD in two independent cohorts. In both cohorts, patients with MAC-LD showed lower ESM_{CSA} together with decreased BMI, while ESM_{MA} was comparable with that of control subjects. Lower ESM_{CSA} and decreased EMS_{MA} were associated with poor prognosis in both cohorts. Among these variables, multivariate analyses showed that decreased ESM_{MA} was independently associated with poor outcome. Importantly, classification based on ESM_{MA} and BMI values provided the best prognostic separations. These results suggest that assessment of body composition changes using the ESM_{CSA}

Table 3
Prediction of Mortality in Patients with mycobacterium avium complex lung disease by Univariate and Multivariate Cox-proportion Analyses.

Predictor	Univariate analysis			Multivariate analysis Model 1			Multivariate analysis Model 2		
	HR	95% CI	p-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age, year	1.059	1.023–1.096	0.0010	1.018	0.974–1.064	0.4241	1.023	0.980–1.068	0.297
Gender, male	4.291	2.265–8.129	<0.0001	4.058	2.114–7.787	<0.0001	4.620	2.390–8.930	<0.0001
BMI, kg/m^2	0.847	0.755–0.950	0.0047				0.854	0.749–0.974	0.0188
BMI, <18.5 kg/m^2	2.928	1.529–5.606	0.0012	1.922	0.907–4.076	0.0883			
ESM_{CSA}, cm^2	0.995	0.955–1.036	0.8087						
ESM_{CSA}, <29.6 cm^2 (male),, <22.5 cm^2 (female)	2.275	1.124–4.605	0.0224	1.098	0.474–2.540	0.8279			
ESM_{MA}, HU	0.973	0.948–0.999	0.0407				0.969	0.939–0.999	0.0473
ESM_{MA}, <38.0 (HU)	2.660	1.438–4.918	0.0018	2.512	1.224–5.156	0.0120			
Species, intracellulare	1.257	0.689–2.2931	0.4558						
Sputum smear, -, ±, 1+, 2+, 3+	1.255	0.958–1.646	0.0995						
Hb, g/dl	0.7780	0.631–0.964	0.0216						
CRP, mg/dl	1.560	1.320–1.842	<0.0001						
TP, g/dl	1.029	0.601–1.762	0.9180						
Alb, g/dl	0.286	0.172–0.473	<0.0001						

BMI; body mass index, ESM_{CSA}; cross-sectional area of elector spine muscles, ESM_{MA}; muscle attenuation of elector spine muscles, NB; nodular/bronchiectatic, FC; fibro-cavitary, Hb; hemoglobin, CRP; C-reactive protein, TP; total protein, Alb; alubumin.

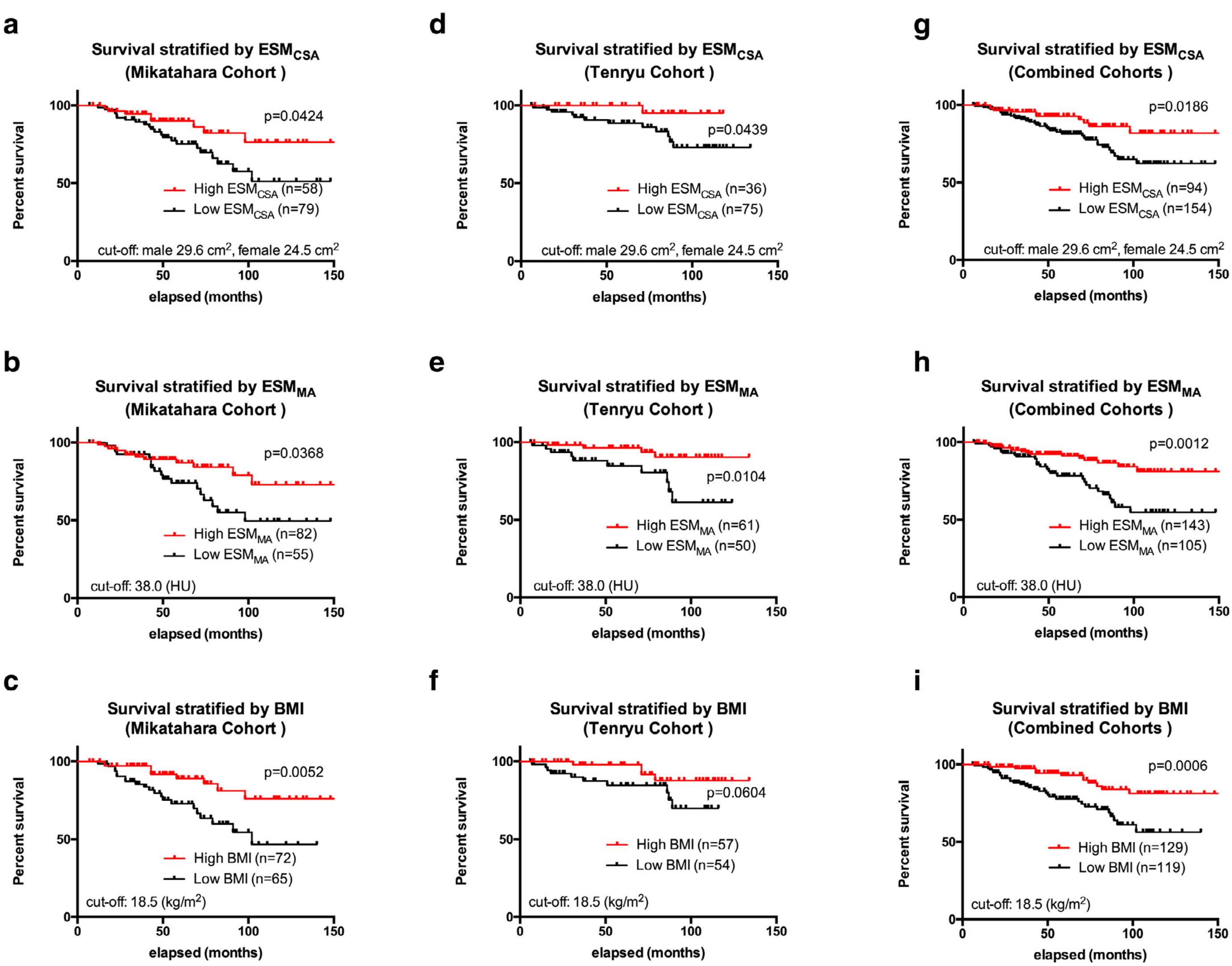

Fig. 2. *Prognostic impact of body composition changes in the prognosis of MAC-LD.*
Kaplan–Meier curves of patients with MAC-LD in the Mikatahara cohort (**a–c**), Tenryu cohort (**d–f**), and combined cohorts (**g–i**) according to ESM_{CSA}, ESM_{MA}, and BMI. p-values were determined by the log-rank test.
MAC-LD: *Mycobacterium avium complex* lung disease, ESM: erector spinae muscles, CSA: cross-sectional area, MA: muscle attenuation, BMI: body mass index.

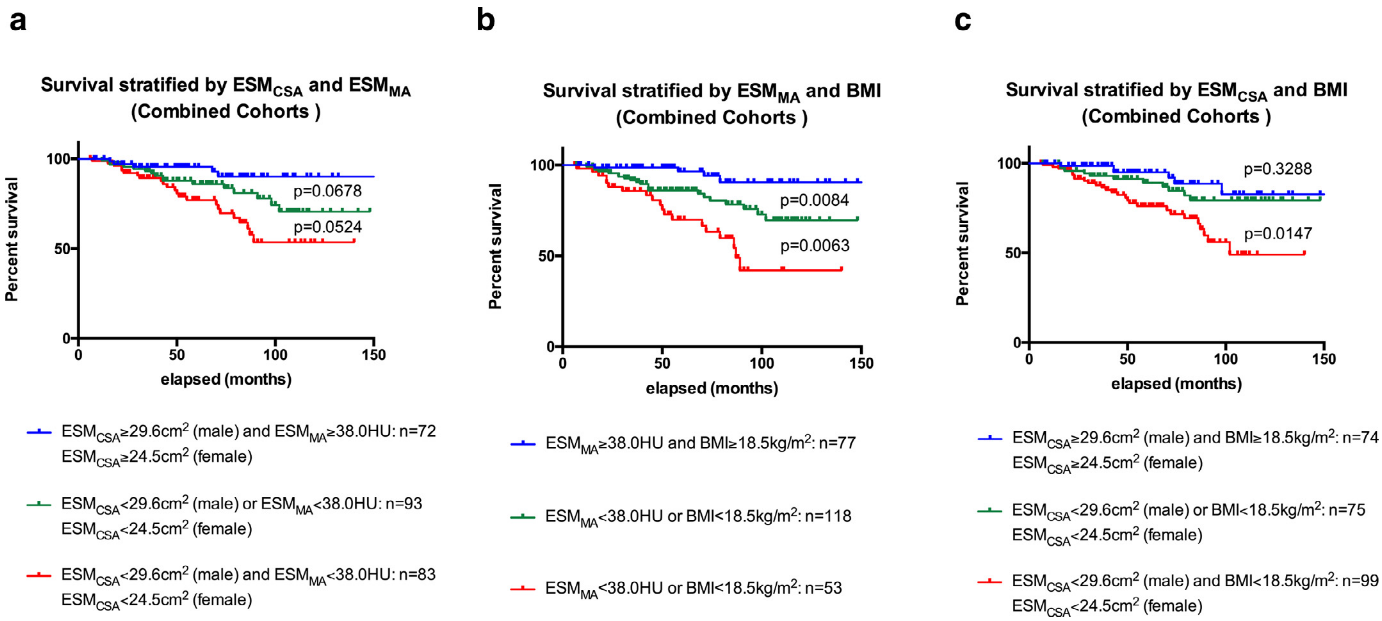

Fig. 3. Kaplan–Meier curves of patients with MAC-LD according to ESM_{CSA} and ESM_{MA} (**a**), ESM_{MA} and BMI (**b**), and ESM_{CSA} and BMI (**c**). p-values were determined by the log-rank test.
MAC-LD: *Mycobacterium avium complex* lung disease, ESM: erector spinae muscles, CSA: cross-sectional area, MA: muscle attenuation, BMI: body mass index.

and ESM_{MA} may predict prognosis and thus be useful for the management of patients with MAC-LD.

Loss of skeletal muscle is a hallmark of cachexia. Body composition changes evaluated with imaging analyses, such as CT and MRI, are surrogate quantitative markers of cachexia. Indeed, previous studies have shown that skeletal muscle loss and its qualitative changes, which were assessed by ESM_{CSA} and ESM_{MA}, respectively, were related to disease progression and subsequently to outcomes.[13,18,19,21] In patients with MAC-LD, lean body images, lower BMI, and progressive weight loss are often observed, and has been shown to have prognostic value.[1,5–10] However, few studies have assessed body composition changes in patients with MAC-LD.[22] The present study showed marked decline of the ESM_{CSA} in patients with MAC-LD in both cohorts, compared with controls, which may be associated with an accelerated hyper-catabolic state in the context of an inflammatory response caused by persistent infection. Importantly, patients with smaller ESM_{CSA} showed poor prognosis.

Conversely, ESM_{MA} did not significantly differ between patients with MAC-LD and controls. However, much wider variability together with higher proportions of subjects with ESM_{MA} less than 20 HU was found in patients with MAC-LD than in controls. Pathological variation in muscle attenuation on CT reflects excess fat deposition in the tissue and is observed in people with obesity, type II diabetes, myositis, and cancer.[23] Thus, lipid deposition leads to decreased ESM_{MA} levels, while loss of fat mass causes increased ESM_{MA} levels. In the present study, significant correlations were found between ESM_{MA} and ESM_{CSA}, and no significant relations were observed between ESM_{MA} and BMI levels. These results suggested that skeletal muscle loss (decreased ESM_{CSA}) and fat deposition (decreased ESM_{MA}) were progressing simultaneously. Meanwhile, there were at least two patterns in patients with MAC-LD with advanced cachexia; weight loss with fat deposition (decreased BMI together with decreased ESM_{MA}) and weight loss with loss of fat mass (decreased BMI without ESM_{MA} decline). Collectively, these results suggested measuring BMI is not enough to assess cachexia in MAC-LD. Interestingly, the patients with cachexia in the former category showed worse survival (Fig. 3b), and the ESM_{MA} values had the highest prognostic power in multivariate analyses, suggesting that lipid accumulation or fat infiltration in the muscles is closely associated with poor prognosis in patients with MAC-LD. Therefore, quantitative measuring the ESM using CT, that enables to evaluating morphological changes in skeletal muscle area as well as lipid deposition, has merit in this point. There is growing evidence that accumulated lipids in skeleton muscle are involved in regulating muscle mass and function.[24] Saturated fatty acids have detrimental effects on muscle function by inducing insulin resistance, reactive oxygen species, and inflammatory signals and by activating proteolysis and impairing protein synthesis and mitochondrial function.[24] Thus, the lipid accumulation or fat infiltration in skeleton muscle suggested by low ESM_{MA} in patients with MAC-LD may further impair physical mobility or activity, which is possibly related to outcome.

To date, only one report has examined skeletal muscle changes in patients with MAC-LD.[22] Contrary to our results, Asakura and colleagues showed that the ESM_{CSA} did not differ between patients with MAC-LD and controls, but a low ESM_{CSA} was significantly associated with all-cause mortality. However, the prognostic significance of ESM_{MA} was not identified. These differences might be partly attributable to variations in the observation periods, patient age ranges, and mortality rates between the two studies. Compared with Asakura's study, ours had a 2-year longer observation period, 5-year-older subjects on average, and an 8%-higher mortality rate.

We further proposed a combination assessment with cachexia-related measurements for precisely predicting the prognosis of patients with MAC-LD. Among the variables, a combination of ESM_{MA} and BMI yielded the best prognostic separations; patients with MAC-LD with decreased ESM_{MA} and low BMI had the worst prognosis. In our cohort, indeed, 14 of 21 patients who died of MAC-LD progression were categorised into the group of decreased ESM_{MA} and low BMI. Although several risk factors for progressive disease and/or mortality in patients with MAC-LD have been reported, including cavity disease, BMI, and number of lung segments involved,[1,5–10] our study provided additional composite parameters and may thus contribute to the further improvement of predicting outcome in MAC-LD. Assessment of cachexia-related factors such as a combination of ESM_{MA} and BMI could add more accurate prognostic information and may also help in decision making for administration of antibiotic treatments.

In fact, cachexia is considered as systemic paraneoplastic phenomenon with cancer patients, beyond the just los of skeletal muscle mass. Thus several molecules ghrelin-receptor agonist (anamorelin)[25] and a selective androgen receptor modulator (enobosarm),[26] have been proven to be effective in patients with cancer. Further, early multimodal interventions with exercise interventions and nutrition supports had shown excellent feasibilities in patients with elderly advanced cancer receiving concurrent chemotherapy.[27] Importantly, very recent protocol-guided individualized nutritional supports had improved survivals for inpatients at nutritional risk, including infectious disease and neoplastic disease, by randomized multicenter study.[28] Therefore, assessments of ESM together with BMI might be utilized for surrogate of representing cachexia to extract MAC-LD patients requiring individualized nutrition supports. Subsequently, host-directed comprehensive managements including nutrition supports and exercise interventions might reduce lipid deposition and have potentials to improve prognosis of MAC-LD patients with cachexia.

The present study had several limitations. First, it was retrospective. Although the median follow-up periods were longer than 5.0 years, certain patients were censored and several biases potentially existed. Second, although we set and analysed two independent cohorts, the numbers of patients may have been insufficient to derive definite conclusions. Third, there were several differences between two cohorts in terms of frequencies of smear positivity, guideline-based therapy, comorbidities, and mortality. There were also several differences between our study and the previous one described above. Additionally, given the retrospective nature of the study, longitudinal changes were not evaluated. To overcome these limitations, further prospective studies with larger cohorts will be required. Especially, the utility of the proposed method for predicting prognosis should be prospectively examined.

In conclusion, the present study examined body composition changes and their associations with prognosis in MAC-LD. Patients with MAC-LD showed skeletal muscle loss together with lower BMI levels, while muscles attenuations were comparable to that of control subjects. Although smaller ESM_{CSA} and lower BMI were associated with poor prognosis, reduced muscle attenuations showed the highest prognostic value in the multivariate analyses. Additionally, the combination of ESM_{MA} and BMI yielded the best prognostic separation. These results warrant further investigation to determine the clinical usefulness of assessing body composition changes on CT in MAC-LD.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

CRediT authorship contribution statement

Daisuke Akahori: Data curation, Formal analysis, Writing - original draft. **Yuzo Suzuki:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing - original draft, Writing - review & editing. **Koushi Yokomura:** Data curation, Formal analysis. **Masahiro Shirai:** Data curation, Formal analysis. **Hideki Yasui:** Data curation. **Hironao Hozumi:** Data curation. **Masato Karayama:** Data curation. **Kazuki Furuhashi:** Data curation. **Noriyuki Enomoto:** Data curation. **Tomoyuki Fujisawa:** Data curation. **Yutaro Nakamura:** Data curation. **Naoki Inui:** Data curation. **Hiroshi Hayakawa:** Data curation, Formal analysis. **Takafumi Suda:** Conceptualization, Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.07.014.

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