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FULL PAPER

Is a radiological score needed to define the severity of Nontuberculous mycobacteria lung disease?

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SUMMARY

High-resolution CT-scan (HRCT) plays a major role in the diagnosis of Nontuberculous mycobacteria lung disease (NTM-LD), but its role in follow-up is controversial. Our aim was first to conceive a radiological score able to quantify the severity of pulmonary involvement by NTM infection and, second, to check its association with the NTM-LD clinical burden. We also intended, if possible, to verify the potential influence of NTM specific treatment on the radiological score.

We retrospectively collected the clinical, microbiological and radiological data of all patients who were admitted to our hospital from 1 January 2012 to 1 January 2020 with a confirmed diagnosis of NTM-LD. A radiological score was applied to evaluate lung involvement on HRCT at diagnosis and at 6-18 months follow-up.

Twenty-eight patients with NTM-LD performed follow-up HRCT. No association was found between radiological and clinical score (Spearman R -0.05, 95%CI -0.41 to 0.33). Repeated measures analysis showed a significant increase in radiological score over time (change 1.11, 95%CI 0.10 to 2.11; p-value 0.032), while Mann-Whitney test did not show any difference between treated and untreated patients (p value 0.922).

Further studies are needed to assess the usefulness of routine radiological follow-up in patients with NTM-LD.

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INTRODUCTION

Nontuberculous Mycobacteria (NTM) are ubiquitous in the environment and include more than 180 species. NTM are responsible mainly for diseases of the lung (NTM-LD), but also of skin and soft tissues, lymph nodes and blood (Johnson, Odell 2014; Falkinham 2015).

Although considered a rare disease, the burden and mortality of NTM-LD has been increasing in the last decades, especially in patients with underlying lung disease or immunosuppression in Western countries (Diel *et al*., 2017; Mirsaeidi, Machado 2014).

The latest guidelines of the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious diseases (ESCMID), and Infectious Diseases Society of America (IDSA), jointly endorse specific criteria for the diagnosis of NTM-LD, which relies on clinical, microbiological and radiological data (Daley *et al*., 2020).

Once the diagnosis has been confirmed, it is necessary to decide whether to treat the affected patient. Hence, since the treatment of NTM-LD infections requires multiple long-term antibiotic treatment (Daley *et al*., 2020; Kamii *et al*., 2018), the risk-reward of starting such a treatment must always be carefully

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weighed, especially considering the well-known risks of both toxicity and suboptimal cure rate (Jankovic *et al.*, 2019).

Besides typical respiratory symptoms, positive cultures of sputum, bronchial lavage and/or pleural fluid, or biopsy with typical mycobacterial histopathology (Koh *et al.*, 2013), with regard to radiological data, performing a lung high-resolution computed tomography (HRTC) scan is still considered of paramount importance for patients with a suspected NTM-LD.

However, NTM-LD lesions are extremely varied, including nodular infiltrates, small and multiple nodules, bronchiectasis or cavities (Kim *et al.*, 2005; Provoost *et al.*, 2018), and occasionally it becomes difficult to trace specific lesions back to NTM, especially in patients with underlying chronic lung conditions. What is even more controversial, then, is the role of HRTC for NTM-LD follow-up (Provoost *et al.*, 2018; Moon *et al.*, 2019). Although not invasive, HRCT is certainly costly and a source of considerable radiation exposure for patients. For this reason, if it were not essential either for the diagnosis or for the follow-up of such a disease, the cost would primarily accrue to the patients, and, subsequently, to the health-care system.

The goal of this study is firs to propose a reproducible and objective radiological score, able to quantify the severity of pulmonary involvement by NTM infection, which currently appears as an unmet clinical need. Second, we want to check its association with the clinical burden of NTM-LD. We also intend, if possible, to verify the potential influence of specific NTM treatment, whether it is performed or not, on this novel radiological score.

METHODS

Design and patients

This is a retrospective study conducted at the Foundation IRCCS Policlinico San Matteo of Pavia, a large tertiary-care teaching hospital in Northern Italy. We collected the clinical, microbiological and radiological data of all patients hospitalized with a confirmed diagnosis of NTM-LD from 1 January 2012 to 1 January 2020.

The study included only adults, and written informed consents were provided at admission by all the subjects included in the study. This study was approved by the Ethics Committee of I.R.C.C.S. Policlinico San Matteo Foundation, Pavia, Italy.

NTM-LD was diagnosed if the patient presented compatible clinical symptoms, microbiological data and radiological findings, as specified by the available guidelines. The diagnoses were confirmed by 2 different clinicians, generally Infectious Diseases and Lung Diseases specialists.

Medical records were reviewed and anonymized data was abstracted on standardized data collection forms.

Demographic data include age and sex, while clinical data include comorbidities, symptoms on admission, antimicrobial treatment and outcome. Microbiological data, such as NTM species identification (where available) and radiological data (HRCT results) were collected as well.

The patients were then considered treated if they received at least two effective antimicrobials for more than 6 months.

Among these patients with NTM-LD, we retrospectively identified those who performed an HRCT at baseline, defined as the time of NTM infection diagnosis (Time 0, T0) and a subsequent HRCT at a follow-up time, 6-18 months later (Time 1, T1).

HRCT images were carefully reviewed by 4 different radiologists, who quantified lung involvement with an *ad hoc* radiological score, thoroughly described below.

The overall scores at HRCT baseline and follow-up were matched in order to objectively compare the progress of lung involvement, if applicable. Significantly, all the radiologists were stringently unaware of the patients' treatment status. Thus, we were able to estimate the difference in the radiological scoring values, and consequently in the NTM-LD, in patients who were specifically treated for NTM and in those who were not treated at all, without any influence on the radiologists' evaluation.

To facilitate the analyses, we extrapolated from the comprehensive score (which we named complex score) a simplified version of this score, properly named simple score. The lung segments were attributed with a straight value of 0 or 1, corresponding to the absence or the presence of any lesion, respectively. Then, we summed up the values of all the segments.

To be confident of the effectiveness of such simplification, consistency between both scores was tested.

Furthermore, to define the overall severity of the lung disease, for each patient we counted the number of signs and symptoms among those highlighted in the published researches as being an expression of higher NTM-LD severity.

Specifically, we assigned 1 point to each of the following characteristics: age >65 years, female sex, BMI <18, history of COPD, diabetes, HIV infection, past and actual neoplasia, solid organ or bone marrow transplant, as well as symptoms such as persistent cough, dyspnea, and fever (TC >37.7°C). Finally, microbiological data were also considered, since some species are unequivocally accountable for a more serious disease than others. Hence, *M. abscessus, M. avium, M. intracellulare, M. kansasii, M. xenopi*, and *M. chelonae* were considered at higher risk than the others. Their sum represented the clinical severity score.

Radiological Methods

The HRCT examinations were retrospectively reviewed by 4 different experienced radiologists in order to reach a mutually agreeable reading.

A quantitative radiological score was developed by modifying previously published scoring systems.

According to the Boyden Classification, the lung parenchyma was subdivided in eighteen segments (Chassagnon *et al*., 2016).

In each lung segment, both the presence and the extent of consolidation areas, solid nodules, ground glass opacities, bronchiectasis, bronchial wall thickening, atelectasis, bronchial filling and distal bronchiolar filling were noted.

The extent of consolidation areas, ground glass opacities, bronchial wall thickening, atelectasis, bronchial filling, and distal bronchiolar filling separately contributed to the final score as follows: 1 point if 1-25% of the segment was involved, 2 points if 25-50% of the segment was involved, 3 points if 50-75% of the segment was involved, and 4 points if more than 75% of the segment was involved.

Parenchymal involvement	<25%	25-50%	50-75%	75-100%
Points	1	2	3	4

Bronchiectasis was classified in 3 degrees which contributed to the score with 1, 2 and 3 points respectively: mild, if the bronchial lumen was slightly greater than the adjacent vessel, moderate if the luminal diameter was 2-3 times the diameter of the adjacent vessel, and severe if the luminal diameter was greater than 3 times the diameter of the adjacent vessel.

Severity of bronchiectasis	*Absent*	*Mild*	*Moderate*	*Severe*
Points	0	1	2	3

For each segment, the presence or absence of lung nodules (≥10 mm) accounted for 1 or 0 points, respectively. The presence of cavities added one more point to the score for each segment involved.

We also derived a simplified version of this score for easier clinical use, where each of the radiographic findings is scored as 1 at each of the 6 pulmonary lobes and as 0 otherwise. The score is computed as the sum of the lobar scores, both overall and by specific lesion.

Microbiological study

When mycobacterial culture was requested by the physician ordering the exam, all the specimens underwent decontamination with 0.25% N-acetyl-L-cysteine and 1% NaOH (NALC-NaOH). The decontaminated samples were inoculated both in liquid medium using an automated system (Mycobacteria Growth Indicator Tube (MGIT); BD Biosciences, Sparks, Maryland, USA), and on solid medium (Löwenstein-Jensen). The inoculated media were incubated at 35°C for up to 8 weeks.

Positive samples were identified by staining with Kinyoun, morphologic evaluation and biochemical tests. Starting in 2014, identification was performed by using Genotype tests (Hain - distributed in Italy by Arnika) and Matrix-Assisted Laser Desorption Ionization Time-Of-Flight (MALDI-TOF) (Bruker Daltonik GmbH, Bremen, Germany). Drug sensitivity tests were performed using broth microdilution tests by the Sensititre System (TREK Diagnostic Systems Waltham, USA). Minimum inhibitory concentration (MIC) was interpreted according to breakpoints as recommended by Clinical and Laboratory Standards Institute (CLSI) guidelines.

Statistical Methods

Descriptive statistics were computed for all variables assessed in the study population. Mean and standard deviation were used for normally distributed variables, median and interquartile range for skewed distributions, proportions for categorical variables.

Continuous variables were compared using the exact Mann-Whitney U test. The Fisher's exact test was used to compare proportion. The Spearman R was used to measure association (with 95% confidence interval, 95% CI).

Generalized linear regression analysis for repeated measures with clustered standard errors to account for intra-patient correlation were used to show changes in the simple score from the baseline- to the follow-up HRCT. The change and 95% CI are reported.

Furthermore, to assess if there was a difference in clinical score between patients who performed a follow-up CT scan and those who did not, we performed the Wilcoxon rank-sum (Mann-Whitney) test.

Stata 16 (StataCorp, College Station, TX, USA) was used for computation. A 2-sided p-value <0.05 was considered statistically significant.

RESULTS

In total, 172 patients with NTM infection were recruited. Among them, 87 were females and 85 were males, with a mean age of 64.75 years (SD±15.12). Only 28 patients performed a follow-up HRCT 6-18 months after the baseline HRCT (T1). Therefore, only these patients were included in the main analysis.

Demographic and clinical data, such as clinical and radiological scores before and after treatment, for these 28 patients are shown in *Table 1*.

The Spearman rank test showed a strong association between complex score and simple score (R=0.82, 95% CI: 0.65 to 0.92). No association between the clinical and radiological simple score at presentation

Table 1 - *Demographic and clinical characteristics of study population.*

	Total =28 patients (%)
Age >65, N (%)	14 (50%)
Female, N (%)	15 (53.57%)
Specimen	
Sputum, N (%)	7 (25%)
Bronchioalveolar lavage, N (%)	18 (64.29%)
Other, N (%)	3 (10.71%)
Cough, N (%)	15 (53.57%)
Fever, N (%)	8 (28.57%)
HIV infection, N (%) (Missing data =7)	0 (0%)
Diabetes mellitus, N (%) (Missing data =1)	1 (3.70%)
COPD, N (%) (Missing data =1)	13 (48.15%)
CF, N (%) (Missing data =1)	0 (0%)
SOT or HSCT recipient, N (%) (Missing data =1)	2 (25%)
Malignancy, N (%) (Missing data =1)	6 (22.22%)
Treatment, N (%) (Missing data =2)	20 (80%)
Species	
M. abscessus, N (%)	3 (10.71%)
M. avium, N (%)	11 (39.29%)
M. gordonae, N (%)	2 (7.14%)
M. intracellulare, N (%)	3 (10.71%)
M. kansasii, N (%)	5 (17.86%)
M. xenopi, N (%)	2 (7.14%)
Non identified Mycobacterial species, N (%)	2 (7.14%)
Clinical score T0, M (SD)	3,96 (1.53)
Complex score T0, M (SD)	30,32 (24.68)
Complex score T1, M (SD)	33,11 (28.82)
Simple score T0, M (SD)	11.8 (6.9)
Simple score T1, M (SD)	12.9 (7.6)

HIV = human immunodeficiency virus, COPD = chronic obstructive pulmonary disease, CF = cystic fibrosis, SOT = solid organ transplant, HSCT = hematopoietic stem cell transplant, M. = Mycobacterium, M. spp = Mycobacterium species, tbc = tuberculosis.

Table 2 - *Two sample Wilcoxon rank-sum (Mann-Whitney test) for radiological simple score by components of clinical score.*

Simple score	*Mean (SD)*	*Exact p-value*
Age		
≤65	11.0 (7.1)	0.49
>65	12.6 (6.9)	
Sex		
male	10.5 (6.8)	0.23
female	12.9 (7.1)	
BMI		
<18	8.0 (3.6)	0.42
≥18	12.2 (7.5)	
COPD		
Yes	12.7 (7.6)	0.56
No	10.9 (6.7)	
Diabetes mellitus		
Yes	10.0 (1.0)	0.85
No	11.8 (7.2)	
Cough		
Yes	10.9 (6.9)	0.44
No	12.8 (7.2)	
Fever		
Yes	12.9 (9.1)	0.96
No	11.3 (6.1)	
Dyspnea		
Yes	10.9 (8.1)	0.30
No	12.3 (6.4)	
Tumor		
Yes	10 (7.5)	0.35
No	12.3 (7.0)	
SOT recipient		
Yes	10.0 (1.0)	0.78
No	11.9 (7.3)	
Species		
Yes	11.8 (6.9)	0.72
No	11.5 (8.6)	

BMI body mass index, COPD chronic obstructive pulmonary disease, SOT solid organ transplant, Species refer to M. abscessus, M. avium, M. intracellulare, M. kansasii, M. xenopi and M. chelonae.

(Spearman R -0.05, 95% CI: -0.41 to 0.33) or with the clinical and radiological complex score (Spearman R 0.002, 95% CI: -0.371 to 0.375) was noted.

With regard to the difference in clinical score between patients who performed a follow-up CT scan and those who did not, we found a higher clinical score in the latter group (mean ±SD, 3.19±1.65; 3.93±1.53; p value 0.019).

Similarly, there was no difference in the radiological simple score according to the presence or absence of each variable of clinical score (*Table 2*).

We observed a significant increase in the simple score at follow-up HRCT (change 1.11, 95% CI: 0.10 to 2.11; p-value 0.032), while an increase in the radiological complex score at follow-up was documented but the difference did not reach statistical significance (change 2.79, 95% CI: -3.02 to 8.59; p-value 0.333).

No significant difference in the simple score variation between treated and untreated patients was found by using the Mann-Whitney test [median changes 2 (25^{th}-75^{th} -3 to 6) and 1 (25^{th}-75^{th} 0 to 2), respectively; p value 0.922].

DISCUSSION

The present study was conceived and designed to propose a simple, reproducible and objective score able to quantify radiological involvement in NTM-LD

and to answer a currently open issue regarding the association between the HRCT radiological pattern of NTM-LD and its clinical burden.

Although based on small numbers, we failed to identify any association. Moreover, the score values have very little variation in the presence or absence of any of the evaluated clinical characteristics.

Furthermore, we realized in our common clinical practice that there seemed to be little noticeable change in the outcome of those patients who received specific NTM treatment and those who did not.

Although this difference may seem easily detectable from a clinical point of view, it is not equally remarkable from a radiological one. Consequently, the simple score was developed to determine whether there was a definite association between radiological and clinical burden of NTM-LD between treated and untreated patients.

Once again, no association was found. Accordingly, our results are similar to those of a previous study from Provoost *et al*., (2018), which showed no difference in radiological evolution at follow-up between these subsets of patients (Provoost *et al*., 2018).

However, we found a significant worsening in radiological score over time. This data might be attributable to these patients' underlying chronic pulmonary conditions, which are merely more likely to deteriorate over time.

Since there are no pathognomonic tests for diagnosis of NTM-LD, clinical symptoms, radiological and, ultimately, microbiological findings, plus repeated confirmation of the etiologic agent, must be gathered to confirm an NTM infection.

However, NTM-LD symptoms are non-specific, especially because the affected patients frequently suffer from pre-existing and chronic lung diseases (Prince *et al*., 1989).

Therefore, when those patients first come to the clinician's attention and complain of fatigue, cough, dyspnea and chest discomfort, it is rather challenging to determine whether NTM etiology is the leading culprit. Furthermore, fever and weight loss occur less frequently than in patients with typical tuberculosis. Therefore, confirmation of NTM-LD diagnosis is surely a prerequisite, but not enough to decide whether or not to initiate a targeted antibiotic treatment. This is indeed a choice based on a careful risk-benefit analysis, because, as may be readily expected, specific NTM treatment is long and is not devoid of potential toxicity and side effects (Lombardi *et al*., 2021; Daley *et al*., 2020).

Several studies identified some clinical factors potentially associated to poor prognosis and higher risk of progressive lung disease, leading to the prompt start of specific antibiotic treatment (Hwang *et al*., 2017; Jhun *et al*., 2019).

Besides those clinical characteristics, the extent of lung disease on HRCT has also been considered by some authors, with fibrocavitary disease (properly defined as the presence of cavities on the lungs) being significantly worse than nodular/bronchiectasis disease (Hayashi *et al*., 2012; Kwon *et al*., 2019; Oshitani *et al*., 2020).

Some limitations have to be underlined, such as the small number of patients included with NTM-LD and the retrospective and single-center nature of the study design, accounting for several missing data. Other limitations to be acknowledged are selection bias, since follow-up CT-scan may have been limited to more severe patients. To confirm this hypothesis, we compared patients who performed a follow-up CT scan and those who did not, and found that the latter had a higher clinical score. Moreover, different species of NTM may behave in a clinically different manner. We are aware of lack of standard management of this condition's diagnosis, treatment, and information on patient adherence to treatment and follow-up, resulting in significant differences in the physician's decisions.

Nevertheless, in our opinion, this study contributes to greater insight on the diagnostic appropriateness of a highly critical disease. While imperative at the time of diagnosis of NTM-LD, further studies are needed to assess the usefulness of radiological follow-up at 6-18 months, given the high costs and the elevated level of radiation involved.

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Conflicts of interest

The authors have none to declare.

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