Original Article

Differences in pulmonary nodular consolidation and pulmonary cavity among drug-sensitive, rifampicin-resistant and multi-drug resistant tuberculosis patients: a computerized tomography study with history length matched cases

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Background: There have been concerns that literature described radiological feature differences between drug-sensitive pulmonary tuberculosis (DS-PTB) and multidrug-resistant (MDR)-PTB were confounded by that MDR-PTB cases tend to have a longer history. Using history length matched DS-PTB and MDR-PTB cases from a well-defined urban region in Dalian, we retrospectively analysed the CT feature differences of these paired cases with a focus on pulmonary nodular (PN) consolidation and pulmonary cavity (PC).

Methods: There were 33 consecutive MDR-PTB cases [inclusive of rifampicin-resistant (RR) cases, 27 males and 6 females, mean age: 49.2 years], with 19 cases had a history of <1 month and 8 and 6 cases had a history of 1–6 and >6 months respectively. To pair the MDR-PTB cases with history length, matched 33 cases of DS-PTB patients (21 males and 12 females, mean age: 56.5 years) were included. All patients were new PTB without HIV infection. The first CT exams prior to treatment were analysed.

Results: Compared with DS cases, MDR cases had a much higher prevalence of PN (75.76% *vs.* 45.45%) and a higher number of PN per positive case for PN (6.2 *vs.*1.53). For the cases >1 month history, MDR-PTB had a higher number of PC per positive case than that of DS-PTB cases (7.18 *vs.* 2.36). To differentiate DS-PTB from MDR-PTB, receiver operating characteristic (ROC) analysis showed a cutoff PN number of ≥3 had 48.5% sensitivity and 93.9% specificity, and a cutoff PC number of ≥4 had 39.4% sensitivity and 84.9% specificity. The lung field distribution of all lesions tended to be wider for MDR-PTB cases. MDR-PTB cases appeared to be associated with a faster progression in the absence of treatment.

Conclusions: MDR-TB is likely intrinsically more invasive than DS-TB. Multiple PN and Multiple PC are promising signs for the suspicion of MDR-PTB on chest imaging.

Keywords: Differential diagnosis; tuberculosis (TB); multidrug-resistant (MDR); computed tomography; pulmonary

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Introduction

According to the World Health Organization (WHO) report in 2019, tuberculosis (TB) remained the biggest single killer among infectious diseases, with 10 million active TB cases occurred in 2018 which caused 1.5 million cases died (1). The emergence of drug-resistant (DR) TB increases the burden of TB control. Multidrug-resistant tuberculosis (MDR-TB) refers to TB infection resistant to at least two first-line anti-TB drugs, isoniazid and rifampicin. About 0.5 million people developed DR-TB in 2018, of these 78% were MDR-TB, while only 1/3 of the confirmed MDR-TB cases were adequately treated (1). Extensively drug-resistant TB (XDR-TB) is defined as TB that has evolved resistance to rifampin and isoniazid, as well as to any member of the quinolone family and at least one of the second-line injectable drugs: kanamycin, amikacin, and capreomycin. Of MDR-TBs, XDR-TB accounts for 4–20% of these infections (2,3). Recently, a new category of DR *Mycobacterium tuberculosis* (*M.tb*) strain named totally drug-resistant TB (TDR-TB) has been identified, which is resistant to all first- and second-line drugs used to treat TB (4). Moreover, it is estimated that there are 1.9 million latent MDR-TB infected individuals around the world (5). When resistant mutants arise during treatment with anti-TB drugs, it is considered as acquired resistance (previously treated MDR-TB). Patients infected with an already drug-resistant strain develop primary resistance (new MDR-TB), which is observed in newly diagnosed TB patients. It has been estimated that globally 3.5% (which can be much higher in some regions) of newly diagnosed TB patients, and 20.5% of previously treated patients, are MDR-TB (1,6).

Early detection and treatment are important to achieve MDR-TB cure and reduce mortality. For already existing strains of DR *M.tb*, it is vital to halt their transmission in the community or hospital. Despite that a wide range of geno- and phenotypic tests are available to detect DR *M.tb* strains and their susceptibility to drugs used, delay of appropriate MDR-TB treatment is common. Specimens used to detect MDR-pulmonary tuberculosis (MDR-PTB) are mostly sputum and bronchoalveolar lavage fluid, but when effective samples are not available, the utility of existing detection methods is limited. Chest imaging can potentially have an important supporting role for the diagnosis of MDR-PTB (7). The suspicion of MDR/XDR-PTB by chest imaging can further guide and even intensify the diagnostic process for MDR-TB. A number of published articles described the potential imaging features difference between drug-sensitive (DS) and MDR-PTB (7-20). It had been suggested that MDR-TB cases tended to have more extensive disease, more likely to be bilateral, to have pleural involvement, to have bronchiectasis, and to have lung volume loss. XDR-TB overall appears even more aggressive than MDR-TB, with a greater number of cavities, larger cavities, and cavities of thicker wall (7,16,17). However, these signs alone are not sufficient for the differential diagnosis of MDR/XDR-PTB from DS-PTB (7). Moreover, there are many limitations of these reported studies (7). Most studies reported CT data, while patients with the characteristic chest X-ray findings of PTB might not have undergone CT, and in some countries CT scans tend to be performed only in patients with more severe symptoms and signs. For cases reported from tertiary referral hospitals, patients with more severe symptoms or cases that were more complicated might have been selectively included and reported. For comparative studies, the duration of PTB symptoms and signs were usually not well controlled for patients with MDR-PTB or DS-PTB. The variation in imaging manifestations across the studies could be a consequence of differential time intervals between disease onset and chest imaging. There have been great concerns that the observed radiological feature differences between DS-PTB and MDR-PTB were confounded by that MDR-PTB cases tend to have a longer history, thus the differential radiological features shown in MDR-PTB cases may not be intrinsic to MDR-PTB pathology (7).

According to recent literature reviews and our own analysis (7,9,20,21), pulmonary nodular (PN) consolidation and pulmonary cavities (PC) represent the two most promising imaging signs in differentiating MDR-PTB from DS-PTB. Huang *et al.* (9) described that PN, particularly multiple PNs, is more common in MDR-PTB than in DS-PTB, and more common in XDR-PTB than in MDR-PTB. In a chest radiograph study of 11 MDR-PTB cases (8 of them might be post-treatment TB) and 147 DS-PTB cases, Sulistijawati *et al.* (20) reported that PN was the only type of lesions that distinguish MDR-PTB from DS-PTB. Chuchottaworn *et al.* (10) suggested that the characteristics of cavities, including having a maximum diameter ≥30 mm, number of cavities ≥3, and the presence of cavities in ≥2 lung zones, were associated with MDR-PTB (10). In the current study, using history length matched DS-PTB and MDR-PTB cases from a well-defined urban region, we analysed the CT feature differences of these paired cases with a focus on PN and PC. Instead of chest radiograph, in the authors' institution CT is the standard first-line

imaging technique for PTB patients. By removing the confounding factors of history length, primarily we hope to investigate whether pathological processes of DS-PTB and MDR-PTB are intrinsically different. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-145/rc).

Methods

Patient data

This retrospective study was approved by institutional ethics committee at Dalian Public Health Clinical Center (LPSEC2021-009), and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The patient consent was waived due to the retrospective nature of this study. All PTB cases were from the Dalian Public Health Clinical Center, Dalian, China. PTB patients in the urban areas of Dalian are all treated in our center. Data were retrieved from our electronic case archiving system. During the period of June 2018 to September 2021, there were in total consecutive 14 MDR-PTB cases and 19 rifampicin-resistant (RR)-PTB cases with complete disease history. Additional one MDR-PTB and one RR-PTB cases with incomplete disease history were excluded. According to the 2016 WHO update, MDR-PTB management strategy is recommended for all patients with RR-PTB, regardless of confirmation of the isoniazid resistance (22); therefore, in this study RR-PTB is included as MDR-PTB cases. For the 14 MDR-PTB cases, 2 cases, 6 cases, 4 cases, 1 case, and 1 case were resistant to 2, 3, 4, 5, 8 anti-TB drugs respectively. There was no XDR-PTB among our cases.

Among these 33 MDR-PRB cases (hereafter, unless specified, MDR-PTB include RR-PTB cases), 19 cases had a disease history of <1 month or were discovered during a routine health check. Eight and 6 cases had disease history of 1–6 and >6 months, respectively. Disease history refers to the time when the patient noticed his/her respiratory discomfort to the time when he/she was diagnosed as suffering from active TB. To pair the MDR-PTB cases, from our hospital database we retrospectively collect 33 cases of PTB patients who were confirmed to be DS-TB (Table S1). These DS cases were diagnosed and treated in our hospital also during June 2018 to Aug 2021. In total, there were 21 males and 12 females in the DS group, with a mean age of 56.48 years (range, 11–84 years); and 27 males and 6 females in the MDR group, with a mean age of 49.18 years (range, 14–79 years). These 33 pairs of MDR-PTB and DS-PTB cases were also broadly matched in diabetes history (Table S2). All patients were HIV-negative, and none had immunocompromised status.

According to the local standard practice, all patients had CT when suspected to have PTB. The interval between the first CT imaging and drug sensitivity confirmation test had a median of six days. Drug sensitivity confirmation test included a combination of sputum culture and Genexpert test results. For both DS and MDR cases, lung CT was performed with a GE Brightspeed 16-slice spiral CT scanner. The scan parameters included: tube voltage 120 kV, tube current 150 mA, slice thickness 5.0 mm, and pitch 1.38. No contrast agent was administered.

Image analysis

The first CT exams prior to anti-TB treatment were analysed. All PTB lesions were read for their extent. A longitudinal axis was taken from the upper apices of the lungs down to the diagram, and then this axis was divided into three segments of equal length with each segment correlated to a zone. In this way, two lungs were divided into six zones. Modifications were made to the Fleischner Society Glossary definitions for PN and PC (23). A PN was a rounded or oval (but not band-like) solid opacity with a relatively clear boundary measuring between >6 mm and 3 cm in diameter (*Figure 1*), and quantified for their number. Smaller nodules and aggregation of smaller nodules were not counted as PN in this study. A PC was a gas-filled space, seen as a lucency area within pulmonary consolidation or a nodule (*Figure 1*). PC was counted only for those with a lumen diameter >5 mm. Multiple cavities in a single consolidation is counted as one cavity. Worm-eroding like cavity (WELC) is more likely to be numerous, these usually small cavities in one consolidation were together counted as one cavity. A PC with a PN was counted as both one PC and one PN. PC was also differentiated from bulla and cyst with a thin wall. These approaches were designed to facilitate further computer-aided image analysis. CT images were initially read by a radiology trainee (CJZ) who had dedicated training in reading CT of PTB. The final reading was recorded by a specialist radiologist (YXJW).

Statistical analysis

Statistical analysis was processed using GraphPad Prism (San Diego, CA, USA). Comparisons between two groups were

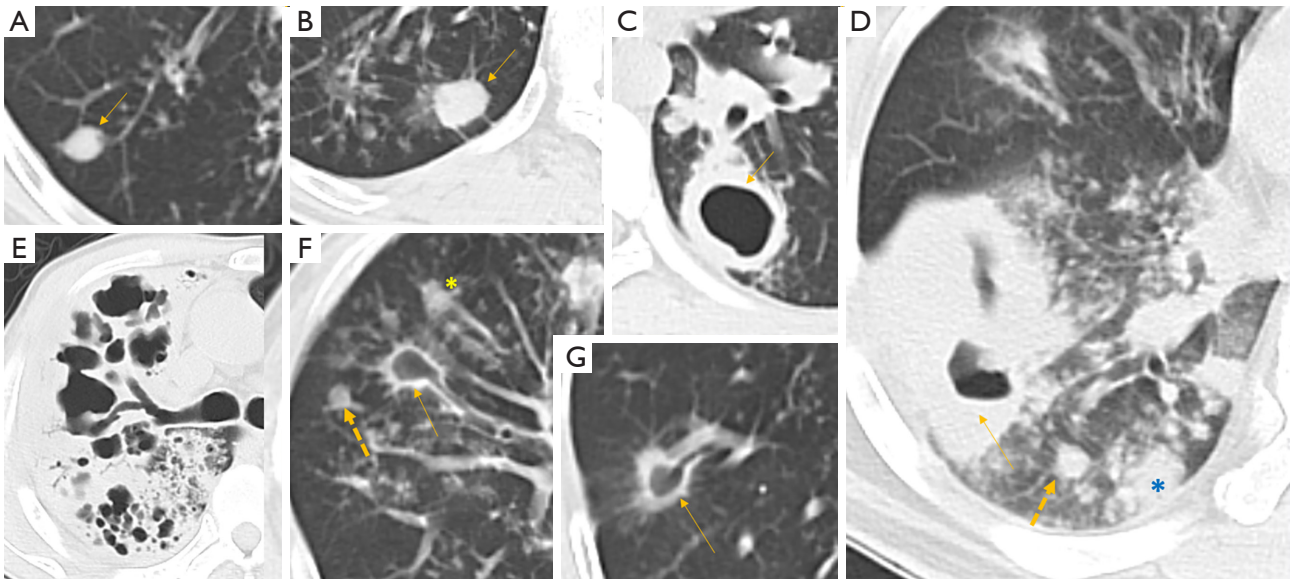

Figure 1 Illustration of PN and PC. (A,B) Arrow indicates a PN; (C) arrow indicates a cavity with a well-defined wall; (D) arrow indicates a cavity and dotted arrow indicates a PN. *, an aggregation of many small nodules (<6 mm) not counted as PN. (E) Multiple worm-eroding like cavities counted as one cavity, the individual small cavities' number was not counted in this study. (F) Arrow indicates a cavity and dotted arrow indicates a PN. *, an aggregation of two small nodules (<6 mm) not counted as PN. (G) Arrow indicates a cavity. PN, pulmonary nodular consolidation; PC, pulmonary cavity.

Table 1 Prevalence (positive rate), mean number per positive case for PN and PC, and mean size for PN

Lesions	History	Prevalence (%)	Mean No. #	Mean size #
DS PN	<1 month	36.84[a]	1.43[b]	14.22±7.97[d]
MDR PN	<1 month	73.68[a]	3.57[b]	12.24±4.83[d]
DS PN	≥1 month	57.14	1.63[c]	11.55±5.56
MDR PN	≥1 month	78.57	9.55[c]	11.66±3.62
DS PC	<1 month	84.21	3.06	
MDR PC	<1 month	78.95	4.27	
DS PC	≥1 month	78.57	2.36[e]	
MDR PC	≥1 month	78.57	7.18[e]	

#, counting per positive case. [a], P=0.049; [b], P=0.001; [c], P<0.001; [d], P=0.107; [e], P=0.003. PN, pulmonary nodule; PC, pulmonary cavity; DS, drug-sensitive, MDR, multidrug-resistant including rifampicin-resistant.

chi-square test for categorical variables and Mann-Whitney U or Wilcoxon signed-rank tests for continuous variable. Pearson test was used for correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance, reporting the area under the ROC (AUROC) and optimal cut-off values with sensitivity and specificity. A P value of less than 0.05 was considered statistically significant.

Results

The DS-PTB *vs.* MDR-PTB differences of prevalence (positive rate) and lesion number for PN and PC is shown in *Tables 1,2*, and *Figure 2*. Even for the cases with a short disease history (<1 month), the PN prevalence difference between DS-PTB and MDR-PTB was apparent (36.84% *vs.* 73.68%, P=0.049). However, there was no significant

Table 2 Mean number per case for PN and PC

History	TB	No. of case	Age (years)	No. of PN	P§ for PN	No. of PC	P§ for PC
≤1 week	DS	10	53.30±18.26	0.70±0.82	<0.001	1.50±1.84	0.487
	MDR	11	46.09±19.38	4.09±5.84		1.36±2.34	
1–2 weeks[a]	DS	5	45.6±22.24	0.6±1.34	0.302	1.00±0.00	>0.999
	MDR	6	56.50±10.71	1.83±2.32		1.00±0.63	
2–4 weeks[b]	DS	6	61.33±9.97	0.33±0.52	0.087	1.17±0.41	0.200
	MDR	3	42.33±29.02	2.00±1.00		3.67±2.31	
>4 weeks	DS	12	61.25±10.99	1.08±1.24	<0.001	1.17±1.40	0.013
	MDR	13	50.00±17.00	6.69±9.59		2.85±3.11	

[a], including 2 weeks; [b], including 4 weeks. P§, P value for comparing DS cases *vs.* MDR cases. PN, pulmonary nodule; PC, pulmonary cavity; TB, tuberculosis; DS, drug-sensitive; MDR, multidrug-resistant including rifampicin-resistant.

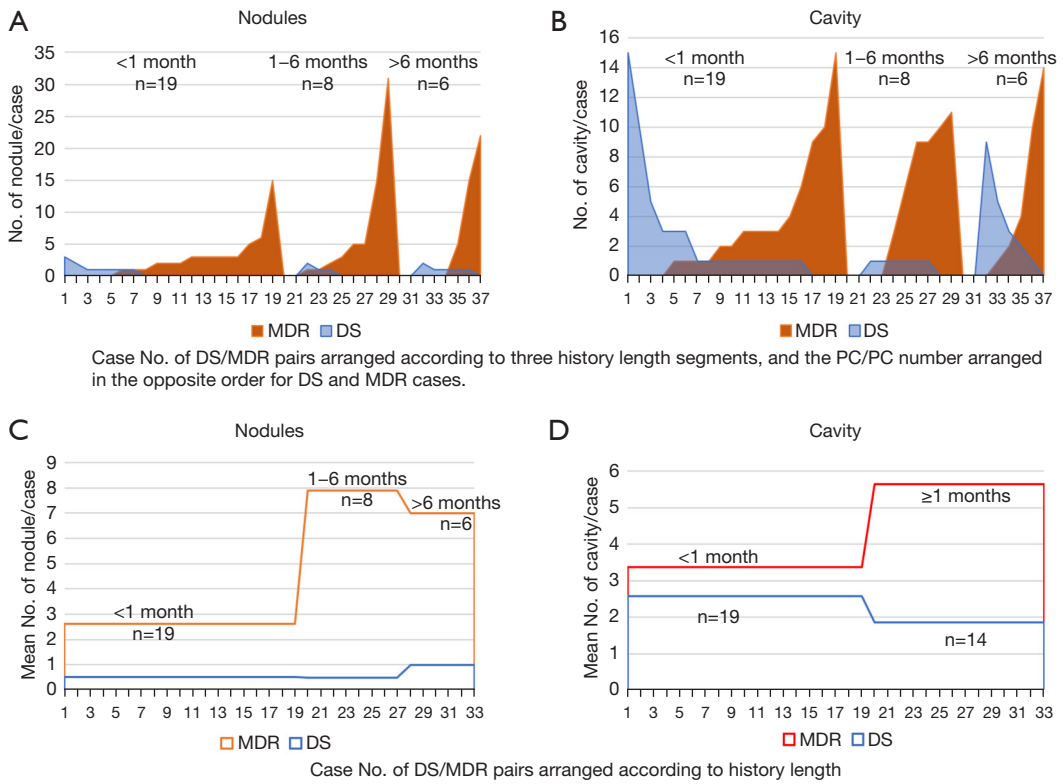

Figure 2 Prevalence (positive rate) and numbers of PN and PC for patients with a history of <1 month, 1–6 months, and >6 months. (A) Number of PN per case; (B) number of PC per case; (C) mean number of PN per case; (D) mean number of PC per case. MDR, multidrug-resistant; DS, drug-sensitive; PC, pulmonary cavity; PN, pulmonary nodular consolidation.

prevalence difference for PC between DS-PTB and MDR-PTB cases. For PN, there was a higher number of PN per positive case among MDR-PTB cases than that of DS-PTB cases. PC number per positive case was broadly similar between MDR-PTB cases and DS-PTB cases for those with <1 month history, while for those >1 months history, MDR-PTB cases had a higher number of PC per positive case than that of DS-PTB cases (7.18 *vs.* 2.36, P=0.003). The

Table 3 Distribution of any tuberculous lesions, PN, and PC

Distribution	PN		PC		Any lesions	
	DS	MDR	DS	MDR	DS	MDR
Bilateral lungs	6.06%[a]	33.33%[a]	15.15%	36.36%	51.52%	66.67%
Lung fields	0.58±0.75[b]	1.79±1.63[b]	1.24±0.97	1.91±1.63	3.52	3.88
Only right lung	21.21%	21.21%	21.21%	21.21%	24.24%	24.24%
Only left lung	18.18%	21.21%	45.45%	21.21%	24.24%[c]	9.10%[c]
R upper field	17.39%	16.77%	14.67%	23.08%		
L upper field	13.04%	16.77%	49.33%	22.38%		
Upper fields (R+L)	30.43%	33.55%	64.00%	45.45%		
R middle field	34.78%	20.65%	4.00%	14.69%		
L middle field	13.04%	20.65%	18.67%	24.48%		
Middle fields (R+L)	47.83%	41.29%	22.67%	39.16%		
R lower field	4.35%	18.71%	4.00%	8.39%		
L lower field	17.39%	6.45%	12.00%	8.39%		
Lower fields (R+L)	21.74%	25.16%	16.00%	16.78%		
PE					27.27%	39.39%
Bilateral PE					9.09%[d]	21.21%[d]

[a], P=0.011; [b], P<0.001; [c], P=0.093; [d], P=0.050. Note some lesions have involved more than one lung field. PN, pulmonary nodule; PC, pulmonary cavity; DS, drug-sensitive; MDR, multidrug-resistant including rifampicin-resistant; PE, pleural effusion.

maximum number of PN for DS-PTB and MDR-PTB was 4, and 31, respectively; while the maximum number of PC for DS-PTB and MDR-TB was both 15. The trend that a longer history was associated higher number of PN and PC was much stronger with MDR-PTB cases than with DR-PTB cases (*Figure 2*).

The distribution of lesions is shown in *Table 3*. PN and PC as well as all lesions tended to be wider for MDR-PTB cases. For all PTB signs, MDR cases were more likely to have bilateral lung involvement, and bilateral pleural effusion was also more common in MDR-PTB cases.

Taking together, MDR-PTB cases appeared to be more extensive during the presentation and also might be associated with a faster progression in the absence of effective treatment (*Figure 2*).

ROC analysis showed the number of PN alone had AUROC of 0.757 for differentiating DS and MDR cases, when cutoff PN number was ≥3, sensitivity was 48.5% and specificity was 93.9%. The number of PC alone had AUROC of 0.636 for differentiating DS and MDR cases, when cutoff PC number was ≥4, sensitivity was 39.4% and specificity was 84.9% (if PC number ≥3, sensitivity: 54.6%, specificity: 72.7%). For MDR cases, numbers of PN and PC lesions were positively and significantly correlated (Pearson r=0.554, P<0.001). For DS cases, numbers of PN and PC lesions were not significantly correlated (Pearson r=0.162, P=0.367). At the individual case' level, there were also overlaps for these parameters (*Figure 3*).

The PN and PC prevalence difference for RR-PTB and real MDR-PTB is shown in Figure S1. With the limitation of small sample size, no apparent trend of difference was observed between RR-PTB and true MDR-PTB cases.

Discussion

There have been concerns that reported radiological feature differences between DS-PTB and MDR-PTB were confounded by that MDR cases tend to have a longer history prior to being diagnosed as MDR, thus the radiological features shown in MDR-PTB may not be intrinsic to MDR-PTB pathology. On the other hand, some studies did not show imaging feature difference between

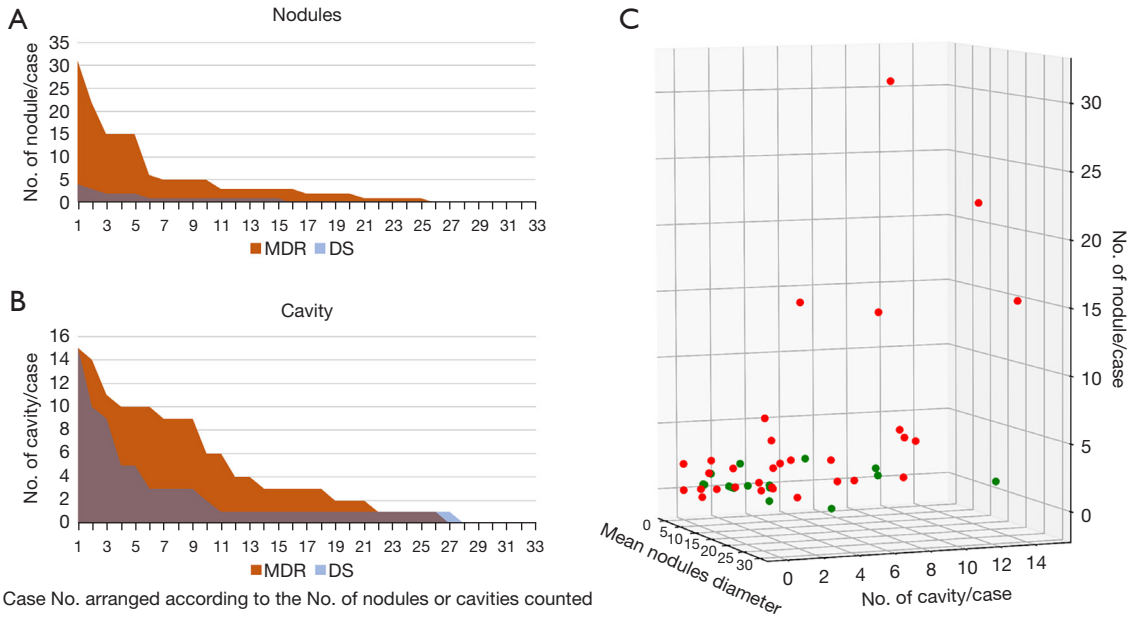

Figure 3 Difference of PN and PC numbers for DS and MDR patients. (A,B) Cases with the largest number of PN or PC are arranged first. (C) Distribution of DS cases (green dots) and MDR (red dots) in a 3-dimensional space with its axis being number of PN, number of PC, and the maximum diameter of PC for each case. A trend of differentiation for DS and MDR cases is noted, but there are also overlaps. MDR, multidrug-resistant; DS, drug-sensitive; PN, pulmonary nodular consolidation; PC, pulmonary cavity.

DS-PTB *vs.* MDR-PTB or did not show imaging feature difference between MDR-PTB *vs.* XDR-PTB (24,25). Our current investigation is the first study on comparative analysis of imaging signs for DS-PTB and MDR-PTB cases with matched history length. Therefore, the imaging feature differences demonstrated in this study are more likely related to the intrinsic pathology process differences between DS-PTB and MDR-PTB. The majority (26/33, 78.79%) of included cases had a well-defined history of <2 months, and all cases were from the same urban region. It is expected that in the future patients will have better access to medical care, thus analyzing cases with a short history will be more relevant.

Our study showed that MDR cases had a much higher prevalence of PN and a higher number of PN per positive case for PN (*Figure 2*). The difference was apparent even for the cases with <1 month history. Our results may be highly relevant, for example, if there would be a PTB patient with coughing for 3 weeks, initial CT shows 5 PNs, then this case would have a high probability of being MDR. For PC, our data did not show difference for patients with history <1 month. However, for those with >1 month history, MDR-PTB cases had a higher number of PC per positive case for PC. Our study further supports the notion that cavity number ≥3 suggests a higher probability of a case being MDR (7,10). This observation is also expected, as it will take time for PC lesions to develop in the infected lungs. Our data also showed overall lesion extent was greater with MDR-PTB cases. Taking these together, our study shows, for the first time, that groupwise MDR-TB is intrinsically more invasive than DS-TB.

Other additional MDR-PTB features were also observed in this study. This study showed a longer history might be associated with higher PN and PC lesion number per case, particularly for MDR cases. It appears that, the lesion progress was more rapid with MDR-PTB cases than DS-PTB cases (*Figure 2*), likely due to the inherent more invasive nature of MDR-PTB. Compared with previous reports, the less difference of PC between DS and MDR cases could be due to that our cases had a shorter history compared with many earlier reports. PN appears to be an earlier change, while it takes time for PC to develop (*Figure 2*). This study further supports the notion we should consider patient history length when analyzing the CT features of PTB patients.

There are many limitations for this study. The first limitation is our relatively small sample size. However, to a certain extent our case number is comparable to many

earlier studies on new MDR-PTB (13-15). The lung zones were not analysed according to anatomical lung segments, and for some 'borderline' lesions, the counts of PN and PC could be associated with a certain degree of subjectivity. It is our long-term goal to develop computer-assisted diagnosis (CAD). The selected signs and definition were designed to facilitate further CAD analysis. Other signs may be helpful for the differentiation of PS-PTB *vs.* MDR-PTB, such as PC cavity size and wall thickness. However, these parameters are difficult to define and measure in many cases. Centrilobular nodules may be another useful sign to evaluate, however, in practice these small changes are also difficult to quantify, and centrilobular nodules may reflect active infection instead of drug sensitivity status (7). Another point is that to differentiate cavity from localized bronchiectasis can be occasionally difficult. While we tried our best to differentiate these two, we cannot be sure we made correction diagnosis for each potential case. However, our results are on groupwise or statistical terms, rather than on absolute term of cavity-by-cavity or case-by-case. This imperfection, if existed, would not affect the overall results of the current study. Our study was a single center study, it is at least theoretically possible that different strains of *M.tb* may be associated with different lung pathology features (26). We plan to collaborate with other medical centers to collect additional data to confirm, or refute, the findings described in this study. It can be argued that history length is a subjective measure by patients themselves. Given the same history length, some patients might have had a longer disease process than others, and the precise disease onset time would remain unknown to the physicians. Up until a certain threshold, more lesions in a patient will prompt this patient to feel ill earlier. However, our approach remains a clinically practical and relevant approach to classify patients. Our study was on new MDR-PTB case among HIV-negative adults. HIV-positive patients and child patients might have different PTB pathology reactions (7,19,27). For MDR-PTB as well as DS-PTB, severe immune suppression may limit the full development of radiologically observable responses to PTB infection (28,29). Since all our cases were new MDT-PTB, whether these features can be generalized to previously treated PTB or child patients should be further investigated. Our earlier literature analysis demonstrated that chest imaging differences of DS-PTB *vs.* MDR-PTB were as prevalent in new MDR-PTB as in previously treated MDR-PTB (7). Finally, the case number in this study might be too small to evaluate the imaging feature difference between RR-PTB and true MDR-PTB. However, clinically RR-PTB is managed in the same way as other MDR-PTB.

In conclusion, our investigation is the first study on comparative analysis of imaging signs for DS-PTB and MDR-PTB cases with matched history length. Our study shows that MDR-TB is likely to be intrinsically more invasive than DS-TB. Compared with history length match DS cases, MDR cases tended to have more extensive lung involvement. Multiple PN and Multiple PC are promising signs for the suspicion of MDR-PTB on chest imaging.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-145/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-145/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-145/coif). YXJW is the founder of Yingran Medicals Co., Ltd., which develops medical image-based diagnostics software. YXJW serves as an unpaid editorial board member of *Journal of Thoracic Disease* from April 2022 to March 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by institutional ethics committee at Dalian Public Health Clinical Center (LPSEC2021-009), and the patient consent was waived due to the retrospective nature of this study.

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Supplementary

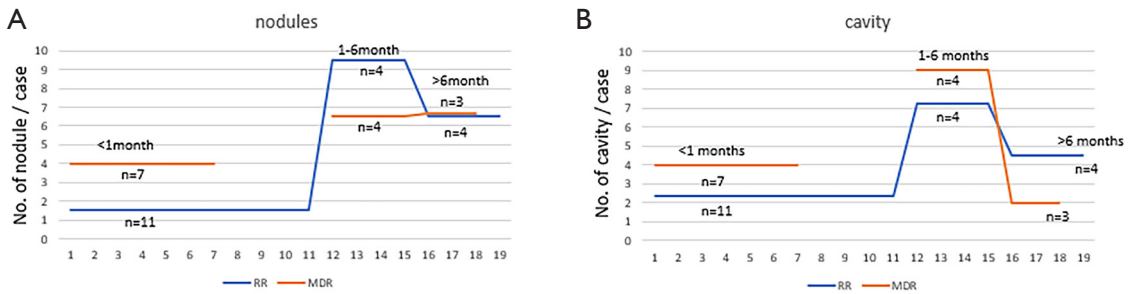

Figure S1 Mean number of pulmonary nodular consolidation (PN) and pulmonary cavity (PC) per positive case for rifampicin-resistant (RR, n=19 cases) and multidrug-resistant (MDR, n=14 cases) tuberculosis patients with a history of <1 month, 1-6 months, and >6 months. No apparent pattern of difference is noted between RR cases and MDR cases.

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Table S1 Tuberculosis disease history length and pulmonary nodule and cavity number of the 33 paired DS (drug-sensitive) and RR/MDR (rifampicin-resistant/ multidrug-resistant) patients

	DS					MDR					
	Sex	Age	History	PN	PC	Sex	Age	History	drugs	PN	PC
Pair 1	F	28	None	0	0	M	60	None	HR	1	0
Pair 2	M	60	2 days	1	3	M	66	1 day	R	3	6
Pair 3	M	69	3 days	1	1	M	29	1 day	R	2	1
Pair 4	M	37	4 days	0	1	F	36	3 days	R	0	0
Pair 5	F	37	4 days	1	10	M	55	3 days	H R S	15	15
Pair 6	M	67	5 days	0	0	M	74	3 days	H R S	3	2
Pair 7	M	84	1 week	2	1	M	28	4 days	R	0	1
Pair 8	M	45	1 week	0	3	M	68	5 days	R	3	0
Pair 9	F	66	1 week	0	0	M	40	5 days	R	2	0
Pair 10	F	61	10 days	0	3	M	43	10 days	H R S E	3	4
Pair 11	F	11	10 days	0	1	M	60	10 days	R	1	2
Pair 12	F	40	1 week	1	1	M	15	1 week	R	3	3
Pair 13	M	51	2 weeks	0	1	M	36	1 week	R	0	9
Pair 14	M	67	2 weeks	0	5	M	44	2 weeks	H R Lfx S	6	3
Pair 15	M	38	2 weeks	3	1	F	58	2 weeks	R	1	3
Pair 16	F	69	2 weeks	0	1	M	67	2 weeks	H R Lfx	0	1
Pair 17	M	54	20 days	0	1	F	67	2 weeks	H R S E	0	3
Pair 18	M	66	20 days	0	1	M	41	20 days	R	2	1
Pair 19	M	55	20 days	1	15	F	14	1 month	H R Lfx	5	10
Pair 20	M	79	1 month	1	1	M	72	1 month	R	5	9
Pair 21	M	53	1 month	0	1	M	55	40 days	R	1	3
Pair 22	M	61	1 month	0	1	M	40	1.5 months	H R S E	5	9
Pair 23	F	43	2 months	0	1	M	62	2 months	R	31	10
Pair 24	F	52	2 months	1	0	M	60	2 months	H R S	15	6
Pair 25	M	65	2 months	0	1	F	29	2 months	R	3	0
Pair 26	M	73	2 months	0	1	F	38	4 months	H R	1	11
Pair 27	M	77	4 months	2	0	M	51	6 months	R	0	10
Pair 28	M	57	6 months	0	5	M	79	6 months	R	2	0
Pair 29	F	69	8 months	1	0	M	63	1 year	[#]	5	2
Pair 30	M	64	1 year	4	3	M	21	1 year	H R S	0	0
Pair 31	F	52	1 year	2	9	M	30	1 year	R	0	1
Pair 32	F	46	6 years^	1	1	M	64	1 year	R	22	14
Pair 33	M	68	10 years^	1	2	M	58	1 year	[¶]	15	4

[#], H, R, S, E, and Pto; [¶], H, R, S, E, Am, Km, Cm and Pto; ^, history length matching was not possible for two MDR case with 1 year history, and two cases with long history were randomly selected. History none, detected during routine health check. H, Isoniazid; R, Rifampicin; S, Streptomycin; E, Ethambutol; Pto, Prothionamide; Am, Amikacin; Km, Kanamycin; Cm, Capreomycin; PN, pulmonary nodular consolidation; PC, pulmonary cavity.

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Table S2 Diabetes mellitus history of the of the 33 paired DS (drug-sensitive) and RR/MDR (rifampicin-resistant/multidrug-resistant) patients

	DS	RR and MDR
None	19 cases	17 cases
History <6 months	3 cases	3 cases
6 month-2 years	2 cases	6 cases
2-10 years	7 cases	4 cases
> 10 years	2 cases	3 cases

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