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Letter to the Editor

Chest X-ray alone is insufficient for predicting drug-resistant pulmonary tuberculosis

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To the Editor,

Chest X-ray (CXR) in combination with machine learning (ML)-based prediction models has been proposed as a promising tool to distinguish drug-susceptible from drug-resistant tuberculosis (DS-/DR-TB) [1,2]. This method builds on the idea that radiological abnormalities differ between patients with pulmonary DS- and DR-TB. Yet, previous studies have yielded conflicting results when comparing CXR findings in clinical practice [3,4]. These studies have, however, also been limited by relatively small sizes or by including few types of drug resistance. The aim of this study was to examine whether CXR findings differ across various types of *Mycobacterium tuberculosis* resistance.

From 2019 to 2022, five subgroups with susceptible, mono-resistant, multidrug-resistant, pre-extensively, and extensively drug-resistant pulmonary TB (PTB) [5], each consisting of 200 Ukrainian patients, were randomly selected from the National Institute of Allergy and Infectious Diseases TB Portal. The database and use of these data have been described in detail previously [6]. Proportions of patients with CXR abnormalities (e.g. cavities, nodules, infiltrates, pleural effusion) in each group were compared using Pearson's chi-squared test and Fisher's exact as appropriate. False discovery rate corrections were calculated and presented as q values to account for multiple testing.

Fifty-five patients (5.5%) were excluded because they had no recorded CXR images, resulting in a cohort of 945 patients in total (Table 1). Their median age was 44 years (interquartile range 36–53, range 4–93) at the time of TB diagnosis. Most patients were males (79%, $n = 746/945$). The description of CXR images was carried out independently by two doctors (a trained radiologist and a TB-doctor i.e. a doctor specialized within the field of phthisiology), and any findings were reported in a standardized form with prespecified variables. When describing radiological images, only study identifiers were used for patient identification. All CXR images were obtained immediately before the patients underwent treatment.

Radiological abnormalities did not differ between groups when accounting for multiple testing (Table 1). For all patients combined, pulmonary cavities were common (41%, $n = 390/945$, 95% CI 38–44%) and most frequently small (<3 cm) (35%, $n = 327/945$, 95% CI 32–38%) and located in upper (34%, $n = 325/945$, 95% CI 31–38%) followed by middle sextants (17%, $n = 163/945$, 95% CI 15–20%). Multiple cavities were seen in 11% ($n = 106/945$, 95% CI 9.3–13%) of patients. A third of patients had infiltrates (32%, $n = 301/945$, 95% CI 29–35%). The infiltrates were most frequently unilateral (26%, $n = 247/945$, 95% CI 23–29%) and located in the upper (23%, $n = 222/945$, 95% CI 21–26%) or middle sextants (16%, $n = 162/945$, 95% CI 15–20%). The number of retreated patients differed significantly across all subgroups ($q < 0.001$), but no findings reached statistical significance when examining only patients with a history

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Table 1
Chest X-ray findings of patients with drug-susceptible and drug-resistant pulmonary tuberculosis in Ukraine from 2019 to 2022

Characteristics	DS-TB ($n = 193$)	Mono-resistant TB ($n = 176$)	MDR-TB ($n = 194$)	Pre-XDR-TB ($n = 187$)	XDR-TB ($n = 195$)	p[a]	q value[b]
Cavities, *n* (%)							
Any cavity	85 (44)	62 (35)	76 (39)	70 (37)	97 (50)	0.032	0.4
Multiple cavities	27 (14)	19 (11)	24 (12)	22 (12)	24 (12)	>0.9	>0.9
Cavity size[c]							
Small	78 (40)	46 (26)	67 (35)	60 (32)	76 (39)	0.031	0.4
Medium	10 (5.2)	16 (9.1)	11 (5.7)	9 (4.8)	22 (11)	0.055	0.4
Large	6 (3.1)	8 (4.5)	7 (3.6)	11 (5.9)	11 (5.6)	0.6	0.8
Anatomical location of cavities							
Upper sextants[d]	71 (37)	51 (29)	63 (32)	59 (32)	81 (42)	0.085	0.4
Middle sextants	37 (19)	25 (14)	31 (16)	26 (14)	44 (23)	0.13	0.4
Lower sextants	3 (1.6)	3 (1.7)	5 (2.6)	4 (2.1)	2 (1.0)	0.8	>0.9
Multiple sextants	24 (12)	16 (9.1)	21 (11)	17 (9.1)	28 (14)	0.4	0.7
Nodules[e], *n* (%)							
Any nodule	180 (93)	167 (95)	175 (90)	178 (95)	178 (91)	0.2	0.5
Multiple nodules	2 (1.0)	1 (0.6)	3 (1.5)	0 (0)	1 (0.5)	0.5	0.7
Infiltrates, *n* (%)							
Any infiltrate	57 (30)	50 (28)	66 (34)	56 (30)	72 (37)	0.3	0.6
Anatomical location of infiltrates							
Unilateral	46 (24)	43 (24)	50 (26)	47 (25)	61 (31)	0.5	0.7
Bilateral	11 (5.7)	7 (4.0)	16 (8.2)	9 (4.8)	11 (5.6)	0.5	0.7
Upper sextants	41 (21)	29 (16)	52 (27)	43 (23)	57 (29)	0.038	0.4
Middle sextants	32 (17)	29 (16)	30 (15)	28 (15)	33 (17)	>0.9	>0.9
Lower sextants	18 (9.3)	13 (7.4)	14 (7.2)	7 (3.7)	12 (6.2)	0.3	0.5
Other, *n* (%)							
Mediastinal lymph nodes affection	73 (38)	50 (28)	61 (31)	64 (34)	50 (26)	0.088	0.4
Lung collapse	5 (2.6)	2 (1.1)	9 (4.6)	2 (1.1)	4 (2.1)	0.2	0.4
Any pleural effusion	22 (11)	20 (11)	24 (12)	19 (10)	23 (12)	>0.9	>0.9
Bilateral pleural effusion	3 (1.6)	2 (1.1)	2 (1.0)	2 (1.1)	2 (1.0)	>0.9	>0.9
Percentage of abnormal lung volume in per cent[f], median (IQR)	22 (10–45)	16 (10–40)	22 (8–46)	18 (9–38)	24 (11–43)	0.6	0.8

DS-TB, drug-susceptible tuberculosis; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

[a] Pearson's chi-squared test and Fisher's exact test as appropriate.

[b] False discovery rate correction for multiple testing.

[c] Small: up to 2.99 cm in diameter, medium: 3–4.99 cm in diameter, and large: >5 cm in diameter.

[d] Sextants were defined as six identical rectangles dividing each lung into three rectangular fields.

[e] Nodules: A nodule refers to a small, rounded area of density on X-ray, defined by a diameter of less than 30 mm.

[f] Abnormal lung volume was estimated by assigning 16.7% to each sextant, with the rater assessing the proportion of abnormal volume in each. The sum of these proportions yielded the total percentage of abnormal volume.

of previous TB (36%, $n = 345/968$, 95% CI 34–40%). Likewise, when comparing DS-TB with XDR-TB alone, no findings reached statistical significance. Adjusting for age, sex, history of TB, and smear positivity in a multinomial regression analysis yielded no statistically significant findings (Supplementary).

In this large study of nearly 1000 Ukrainian patients with DS- and DR-TB, we found no differences when comparing CXR findings. Still, by demonstrating the characteristic radiological abnormalities of TB, our findings highlight the importance of conventional CXR in diagnosing patients with PTB in general. Patients presented with cavities, infiltrates, and nodules located in upper lung fields, a distinctive and well-known presentation of TB that has also been reported with comparable prevalences in other cohorts [2,4]. In contrast, image recognition based on ML has reportedly succeeded in predicting DR-TB from radiological imaging with accuracies between 60% and 70% [1,2]. These studies, which have examined imaging features similar to ours, focused only on one type of DR-TB or grouped several types into a single category. The discrepancy between the relatively high accuracies achieved by such prediction models and the apparent lack of distinctive radiological abnormalities observed in our study highlights that the ability of ML models to detect subtle differences that may not be apparent through conventional observation, thus allowing for more accurate predictions. But, it also demonstrates the challenges associated with the interpretability of ML models and our limited ability to explain the rationale behind its decisions. Hence, it could be questioned whether the ML model predictions reflect an actual causative association between radiological differences and DR-TB, or if they reflect unrecognized bias in the data. If so, applying these findings in clinical practice would pose a risk of falsely identifying patients as having DR-TB, potentially subjecting them to unnecessary treatments with longer regimens that are more often associated with severe adverse events. Consequently, until a better understanding of the rationale behind such predictions is achieved, the clinical relevance of ML models in predicting DR-TB outside of the setting in which they were trained is questionable and should await careful testing in different real-life clinical settings.

In conclusion, this study shows that CXR abnormalities for Ukrainian patients with PTB are distinctive but do not differ among DS- and DR-TB, suggesting that CXR alone is insufficient for predicting drug resistance without the support of novel computational techniques. Cavities, infiltrates, and nodules located in upper lung fields are highly suggestive of PTB, underscoring that conventional CXR is still an essential tool in diagnosing TB. Efforts to scale up the availability of antimicrobial susceptibility testing globally are of utmost importance.

Author contributions

O.S.P.: conceptualization, methodology, formal analysis, data curation, writing—;original draft, writing—review and editing, validation, visualization. T.B.: investigation, writing—review and editing. N.B.: investigation, writing—review and editing. O.A.: investigation, writing—review and editing. N.S.: investigation, writing—review and editing. O.T.: investigation, writing—review and editing. V.K.: investigation, writing—review and editing. A.F.:

conceptualization, methodology, validation, formal analysis, resources, writing—;original draft, writing—review and editing, visualization, supervision. V.N.D.: conceptualization, methodology, validation, formal analysis, resources, data curation, writing—;original draft, writing—review and editing, visualization, supervision, project administration. D.B.: conceptualization, methodology, investigation, resources, writing—;original draft, writing—review and editing, supervision, project administration.

Transparency declaration

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Ethics

This research utilizes publicly available anonymized data from the NIAID TB Portal that did not require ethical approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.05.006.

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