Journal Pre-proof

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PII: S0012-3692(21)01490-2

DOI: https://doi.org/10.1016/j.chest.2021.07.041

Reference: CHEST 4475

To appear in: *CHEST*

Received Date: 24 March 2021

Revised Date: 13 July 2021

Accepted Date: 15 July 2021

Please cite this article as: Jones TP, Dabbaj S, Mandal I, Cleverley J, Cash C, Lipman MC, Lowe DM, The blood neutrophil count after 1 month of treatment predicts the radiological severity of lung disease at treatment end, *CHEST* (2021), doi: https://doi.org/10.1016/j.chest.2021.07.041.

The blood neutrophil count after 1 month of treatment predicts the radiological severity of lung disease at treatment end

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Running title: Neutrophils at one month predict outcome in TB

Conflicts of Interest: Dr. Lowe has received travel and subsistence costs for unpaid consultancy work from CSL Behring, has participated in an advisory board for Merck, and has received research grants from Bristol Myers Squibb, LifeArc and the British Society for Antimicrobial Chemotherapy, all outside the submitted work. All other authors report no conflicts of interest.

Funding: Nil

Prior abstract/presentation: British Thoracic Society Winter Meeting, February 2021

Word counts: Abstract 272, Main text 3321

Abstract

Background: Post-tuberculous lung disease confers significant morbidity. However, the determinants of persistent lung damage in tuberculosis are not well established. We investigated associations between tuberculosis-associated radiological changes and socio-demographic factors, surrogates of bacillary burden and blood inflammatory markers at initiation of therapy and after 1 month.

Research Question: What are the predictors of radiological severity at the end of tuberculosis treatment for tuberculosis?

Study Design and Methods: We collected data from patients treated for drug sensitive pulmonary tuberculosis at our centre over a 5.5-year period. We recorded age, sex, ethnicity, smoking status, symptom duration, sputum smear grade, time to culture positivity and blood results (C-reactive protein and neutrophil count) at baseline and after 1 month of treatment. Chest x-rays performed at baseline, 2 months and end of treatment were assessed independently by two radiologists and scored using a validated system. Relationships between predictor variables and radiological outcomes were assessed using linear or binary logistic regression.

Results: We assessed 154 individuals, mean age 37 years, 63% male. In multivariate analysis, baseline radiological severity correlated with sputum smear grade ($p=0.003$) and neutrophil count ($p<0.001$). At end of treatment, only the 1-month neutrophil count was significantly associated with overall radiological severity in multivariate analysis ($r=0.34$, $p=0.003$), and remained significant after controlling for baseline radiological scores. The 1-month neutrophil count was also the only independent correlate of volume loss and pleural thickening at end of treatment and was significantly higher in patients with persistent cavitation or effusion versus those without.

Interpretation: Persistent neutrophilic inflammation after 1 month of tuberculosis therapy is associated with poor radiological outcome, suggesting a target for interventions to minimise post-tuberculous lung disease.

Tuberculosis (TB) remains one of the most important infectious diseases globally [1]. Although death from acute infection remains significant, the majority of patients are treated successfully achieving microbiological cure with anti-tuberculous therapy (ATT) [1]. However, treated patients often have significant residual lung damage comprising persistent cavities, bronchiectasis and volume loss (including from pleural scarring) [2]. Tuberculosis is thus not only a cause of acute infectious mortality but also of chronic morbidity [3-5] and premature death from later complications. This has been increasingly appreciated recently with the first international symposium on post-tuberculosis lung disease being held in 2020 [6].

Radiological outcome varies even during apparently successful ATT with good adherence. Although more extensive radiological changes at baseline generally correlate overall with those at the end of treatment [2], several studies have documented a diversity of outcomes [7-9].

Attempts to delineate why certain individuals have a more unfavourable prognosis are nascent. There is some evidence that delayed presentation or treatment initiation correlates with poorer resolution of chest x-ray abnormalities [2, 10, 11] although not all studies confirm this [12]. Smoking has also been related to poor treatment outcomes in tuberculosis [13]. The burden of infection (as assessed by sputum smear grade, for example) has been demonstrated to correlate with baseline radiological severity [14] but it is less clear how this relates to abnormalities at the end of treatment.

Neutrophils are key components of the host response to tuberculosis [15], yet often associate with pathology [16, 17]. This cell type and its products released upon cell death – especially neutrophil elastase – are highly implicated in the development of bronchiectasis [18]. Neutrophilic inflammation early in TB disease may therefore lead to more lung damage which will be evident in the radiological appearance at the end of treatment.

Here we aimed to further investigate the associations with radiological outcomes in tuberculosis. In a cohort of patients treated for pulmonary or pleural tuberculosis, we systematically scored chest x-rays and assessed the impact of potential predictors including demographic variables, duration of symptoms, correlates of infection burden and inflammatory markers including neutrophil counts.

Methods

We identified all patients treated for pulmonary or pleural tuberculosis at our centre between January 2009 and June 2014. Patients with mediastinal lymph node tuberculosis were included if there was also documented pulmonary involvement, and patients with disseminated disease were eligible if the lungs or pleura were involved. Patients were excluded if they had HIV infection, drug-resistant tuberculosis (to any of the first-line drug regimen: rifampicin, isoniazid, ethambutol or pyrazinamide), known primary immunodeficiency, were taking immunosuppressive medication or had known pre-existing structural lung disease.

Data were extracted from the departmental and regional databases on age, sex, ethnicity, smoking status and duration of symptoms prior to presentation. Where available, we also recorded treatment interruptions due to medication side effects or patient adherence. The electronic clinical results system was interrogated for neutrophil count at start of treatment and after one month of treatment, C-reactive protein concentration at start of treatment and

after one month of treatment, sputum smear grade and time to tuberculosis culture positivity. Where there was no result available at one month, we selected the sample closest to this time point (median 31 days, IQR 22-39.5 days).

Chest x-rays performed at baseline, after 2 months of treatment (median 61 days, IQR 53-70 days) and at end of treatment were systematically assessed by two specialist respiratory radiologists blinded to patient identification or time point of treatment. X-rays were scored according to a validated system [14], calculated according to the percentage of lungs involved and the presence or absence of cavitation (maximum score=140). Radiologists also measured the maximal cavity diameter, and recorded the presence or absence of effusion, pleural thickening, and fibrosis and volume reduction. Mean scores between the two radiologists were used for continuous variables. Disagreement between radiologists on presence of cavitation or effusion was resolved by consensus. For other binary outcomes, results are presented as 'none' if both radiologists reported the absence of the feature, 'definite' if both radiologists reported the presence of the feature and 'indeterminate' if only one radiologist defined this feature as being present: for analysis, we interpreted 'indeterminate' results as being positive for the radiological feature. Correlation between radiologists for percentage of lung involved was good ($r=0.87$, $p<0.001$) and kappa score for binary outcomes indicated moderate to excellent agreement (0.48 for volume loss, 0.54 for fibrosis, 0.54 for pleural thickening, 0.61 for cavitation, 0.84 for effusion).

Univariate analysis assessing predictors of the radiological scores was performed using Pearson correlation or Spearman rank correlation for continuous variables and t test or one-way ANOVA for categorical variables. All variables with a p-value ≤ 0.1 in univariate testing were used for multivariate analysis via linear regression. Univariate and multivariate analysis of binary outcomes (i.e. presence / absence of a radiological feature at 6 months) were performed using binary logistic regression, again using a threshold of $p \leq 0.1$ to determine

parameters for multivariate. Comparison of neutrophil counts between patients with / without cavities and effusions (or with / without persistence of these features from baseline) was performed by unpaired t test. $p<0.05$ was interpreted as statistically significant. Statistical analysis was carried out using SPSS v27 or GraphPad Prism v8.0.

This research was conducted using information collected by staff within the usual care team as part of routine care (without an intention to use it for research at the time of collection) - as such it did not require formal ethics approval under current guidance from the Health Research Authority, UK.

Results

Patient demographics

154 patients were included in the study, as detailed in Table 1. The mean (± SD) age was 37 (± 16) years and 63% were male. The majority (59%) of patients were sputum smear negative for acid fast bacilli.

A minority of patients experience a deterioration in radiological appearance during tuberculosis treatment; and fibrosis and volume loss are common at the end of treatment

Overall, the chest x-ray severity score decreased from baseline (mean ±SD = 35.8 ±34.8) to 2 months (25.7 ±31.4) and again to the end of treatment (12.3 ± 19.8; Figure 1A). Similar results were observed for the proportion of lungs involved at each time point (Figure 1B). However, a minority of patients (<10%) experienced a deterioration of x-ray score between baseline and 2 months or between baseline and end of treatment (n=10 at both time points; Figure 1C).

Among 55 patients with cavitation at baseline, 23 (41.8%) had persistent cavitation at 2 months and only 11 (20%) had persistent cavitation at end of treatment (Figure 1D and Figure 2A). However, the mean (±SD) cavity size in the patients with persistent cavities at end of treatment only reduced from 3.2cm (±1.6cm) to 2.7cm (±1.7cm) and in 5 (9%) patients the cavity size increased. Notably, there was no difference in the baseline cavity size between patients with persistent cavitation and patients with resolution of cavitation (3.2cm ±1.6cm vs 2.6cm ±1.5cm, p=0.27). There were also five patients with cavitation present on the end of treatment chest x-ray which was not observed at baseline.

Blood inflammatory markers (neutrophil count and CRP) both fell significantly between baseline and 1-month of treatment (Figure 1E & 1F). However, 14/148 (9.5%) patients still had neutrophilia (count >7.5 $x10^9$/L) at 1 month and 76/134 (56.7%) patients still had elevated CRP (>5mg/L); in 16 patients the CRP was still >50mg/L at this time point. Among the patients with neutrophilia at 1 month, 5 were receiving adjunctive corticosteroid treatment and in total 23 patients were using corticosteroids at this time point.

Figure 2 indicates the proportion of patients with cavitation, effusion, pleural thickening, fibrosis and volume loss at each time point. Although the prevalence of cavitation reduced, as described above, and pleural thickening remained broadly stable, both fibrosis and volume loss increased during treatment as anticipated.

Baseline and 2-month radiological severity correlates with sputum smear grade and neutrophil count

We investigated correlates of the baseline overall radiological severity score (Table 2). In univariate analysis, there was a positive correlation with age and a significant effect of ethnicity with higher scores in white patients. There was also a strong effect of sputum smear grade and positive correlations with markers of systemic inflammation (baseline blood

neutrophil count and serum C-reactive protein concentration). However, in multivariate analysis only sputum smear grade and neutrophil count retained significance (Table 2). Analysis of radiological severity of chest x-rays performed after 2 months of treatment revealed similar results (Table 3). Again, age was a significant predictor in univariate analysis but not in multivariate. Sputum smear grade demonstrated a clear association which was also observed in the multivariate model. Baseline inflammatory markers showed some correlation with radiological score, but there were stronger associations with the 1-month neutrophil count and CRP. In the multivariate model only the 1-month neutrophil count retained significance, demonstrating an even stronger relationship with the radiological severity score than sputum smear grade.

Radiological severity at end of treatment is predicted by 1-month neutrophil count

We performed a similar analysis for radiological severity at the end of treatment (Table 4). In an additional analysis, we also included the baseline radiological severity score as a predictor. In univariate analysis, age, sputum smear grade, time to culture positivity and the one-month markers of inflammation (neutrophil count and CRP) were all significant predictors. However, in multivariate analysis only the one-month neutrophil count retained significance ($r=0.34$, $p=0.003$). The baseline radiological severity correlated strongly with 6-month x-ray score, as expected, but was not significant in multivariate analysis; however, the 1-month neutrophil count remained a significant predictor of outcome ($p=0.01$) even with incorporation of the baseline severity score into the model.

As the severity score was originally designed for parenchymal disease, we also performed a sensitivity analysis excluding 35 patients with baseline pleural effusion. Again, the 1-month neutrophil count was the only significant predictor of 6-month severity score ($p=0.01$). The 1-

month neutrophil count also correlated positively with end of treatment score in the 35 patients with effusion (r=0.37, p=0.04).

We proceeded to investigate the predictors of binary outcomes (fibrosis, pleural thickening, cavitation, effusion and volume loss; Supplementary Tables 1-5). The 1-month neutrophil count was a significant predictor in univariate analysis of all outcomes except fibrosis, and it was the only significant predictor observed in multivariate analysis for both volume loss (odds ratio (OR)=1.26 per $1x10^9$ increase in neutrophils, p=0.03) and pleural thickening (OR=1.26, p=0.03).

The 1-month CRP was a significant predictor of all outcomes in univariate analysis, but did not retain significance in any multivariate analyses. Age was a significant predictor in univariate for fibrosis, pleural thickening and effusion, also showing a significant association with pleural effusion in multivariate analysis. Time to culture positivity associated with cavitation in univariate analysis only, as did sex with pleural thickening (less frequent in females).

The neutrophil count at one-month is higher in patients with persistent cavitation at the end of treatment

The one-month neutrophil count was significantly higher in patients with cavitation at the end of treatment versus those without (mean 6.4 ±3.7 $x10^9$/L vs 4.2 ±2.2 $x10^9$/L, p<0.001) or with pleural effusion at the end of treatment versus those without (mean 6.1 ±2.7 $x10^9$/L vs 4.3 ±2.5 $x10^9$/L, p=0.02). It was also higher among patients with baseline cavitation who had persistent cavities at treatment end versus those with resolution (mean 7.1 ±4.3 $x10^9$/L vs 4.4 ±2.0 $x10^9$/L, p=0.005); a similar but non-significant trend was seen for persistence versus resolution of effusion; Figure 2.

Treatment interruption did not impact radiological outcome or 1-month neutrophil count

Nine patients were documented to have significant treatment interruption for hepatotoxicity or poor adherence. The mean radiological severity score at end of treatment in these patients was 11.7 versus 12.3 in other patients (p=0.92), and there was no difference in the 1-month neutrophil count (mean 5.2 versus 4.5 $x10^9$/L, p=0.43).

Other patients also had prolonged treatment, for example due to co-existing central nervous system involvement. However, there was no significant correlation between length of treatment and baseline Ralph score, 1-month neutrophil count or end of treatment Ralph score. We also divided the cohort into those receiving <200 days or ≥200 days of therapy (i.e. within the envelope of standard 6 months' treatment). There was no significant difference in baseline or end of treatment Ralph score or 1-month neutrophil count between these groups.

Corticosteroid usage affects the 1-month neutrophil count but not radiological severity at end of treatment

Patients receiving corticosteroids at 1 month (n=23) had significantly higher blood neutrophil counts than those not receiving steroids (7.01 ±3.84 vs 4.10 ±2.17, p<0.0001). However, there was no difference in 2-month or end of treatment radiological severity score between those receiving or not receiving steroids. Notably, there was a significant positive correlation between 1-month neutrophil count and end of treatment Ralph score in those receiving steroids (r=0.61, p=0.006) and those who did not (r=0.33, p=0.0002).

Discussion

The predictors of poor radiological outcome from tuberculosis are largely unknown. We have here demonstrated that the blood neutrophil count after one month of therapy is a robust and independent indicator of radiological severity at the end of treatment, even after controlling for baseline radiological severity and other potential contributing factors.

Post-tuberculosis lung disease can result in chronic respiratory symptoms [3, 4] and also increases future risk of serious illness, including the development of aspergilloma in persistent cavities [19] or acute infectious exacerbations of bronchiectasis. Accordingly, mortality in tuberculosis survivors has consistently been demonstrated to be higher than population controls or their own siblings [20-22], with a particular risk for those presenting with pulmonary tuberculosis [22]. Highly over-represented causes of death in patients with a history of TB include pulmonary infection and lung neoplasms [20-22].

The outcome from tuberculosis varies significantly between patients. For example, Menon *et al* discovered that even amongst patients with 'far advanced' lesions on chest x-ray, 23% are left with 'no lesion' and 30.8% with 'minimal lesions' on plain films after treatment [7]. Lee *et al* noted that while 38/52 patients had cavities visible on high-resolution computed tomography (HRCT) scan at start of anti-tuberculosis treatment, only 18/52 still had cavitation at the end of treatment [8]; conversely, bronchiectasis was seen in 15/52 patients at baseline but in 23/52 by the end of treatment. A similar pattern was recorded by Long *et al*, with a reduction in cavities and an increase in the numbers with bronchiectasis [9]; interestingly, these authors also note reversal of bronchiectasis in one patient.

In our cohort, although most patients experienced an improvement in radiological severity score, a minority (10 patients) suffered a deterioration. Similarly, although there was resolution of cavitation in most patients, some had persistent cavitation with only marginal change in size and occasionally an increase. The proportions of patients with fibrosis and volume loss increased during treatment, although still only affected a minority. Interestingly,

there was only limited change in the proportions of patients with pleural thickening or volume loss between 2 months and end of treatment, suggesting that these changes occur early. Conversely, the proportion with effusions only noticeably reduced after 2 months while fibrosis largely appeared beyond 2 months of treatment. Resolution of cavitation occurred throughout treatment.

Given this heterogeneity of outcomes and the evolution of changes over time, identifying correlates of radiological severity during treatment are important to guide therapeutic interventions and patient information.

We discovered that baseline radiological severity correlated with sputum smear grade (an indicator of bacillary burden) and baseline neutrophil count. This is in agreement with results from others, who have documented that tuberculosis chest x-ray scores associate with neutrophil abundance at baseline [23, 24]. We have also shown that baseline neutrophilia independently predicts mortality in tuberculosis [17], while several animal models have also demonstrated a pathological role for neutrophils in active TB infection [25-27].

Here, we also investigated radiological outcomes at 2 months and end of treatment, finding that the 1-month neutrophil count, rather than the baseline neutrophil count, was the most significant predictor of radiological severity at these later time points. This implies that ongoing or recrudescent inflammation after 1 month of treatment is a particular risk for poor outcome. The independent association in multivariate analysis with neutrophil count rather than C-reactive protein (a non-specific marker of inflammation) directly implicates these cells in the mechanism of lung damage. Experimentally, Ong *et al* have demonstrated that neutrophil-derived MMP8 is key to matrix destruction in pulmonary tuberculosis [28]. The secretion and activity of neutrophil-derived enzymes including MMP-8, MMP-9 and elastase, and the associated degree of matrix destruction, are increased by hypoxia which is common in tuberculosis lesions [29].

In line with these findings, we also observed that the 1-month neutrophil count associated independently with specific radiological outcomes such as volume loss and pleural thickening, and was higher in patients with persistent cavitation at end of treatment versus either those without cavities or those with resolution of cavitation.

A minority of our patients with persistent neutrophilia after one month were receiving corticosteroid therapy which can artificially increase the blood neutrophil count [30]. Notably, neutrophils are already significantly implicated in tuberculosis paradoxical reactions [31-33]. However, we observed a significant positive correlation between 1-month neutrophil count and end of treatment Ralph score in both the group receiving corticosteroids and those who did not. Furthermore, steroid usage itself was not a significant predictor of radiological severity at the end of treatment.

Our study has limitations. (1) It was only conducted at a single centre which, although conferring the advantage that all patients were managed similarly, inevitably limits the generalisation of the findings. (2) This was a retrospective study and, as such, we did not apply a rigorous protocol. However, in our centre care pathways enable us to investigate and treat tuberculosis in a consistent way, with results being available for the majority of patients. (3) CT scans would have provided more detail on radiological severity, but these were not clinically indicated in most patients and, given the radiation dose, would be difficult to justify even in a prospective study. Chest x-rays still provide a significant amount of information, especially when reviewed by specialist radiologists. (4) Although overall agreement between radiologists was good, and consensus was reached on primary outcome parameters, there were discrepant observations for some binary outcomes. This might have been influenced by factors known to affect interpretation of x-rays including patient rotation or radiographs being taken in expiration. (5) We did not have functional outcomes such as pulmonary function tests or 6-minute walk test (6MWT), and these would be important to include in a prospective

study. However, it has previously been reported that the CXR score employed in this work correlates inversely with 6MWT and forced expiratory volume in 1 second (FEV1) and positively with the St George's Respiratory Questionnaire (SGRQ) score, indicating poorer quality of life [14]. (6) It would also be ideal to measure markers of neutrophilic inflammation in respiratory samples, where they can be obtained, although these samples are more heterogeneous than blood. (7) Although significantly associated with x-ray severity score at end of treatment, the 1-month neutrophil count cannot fully explain radiological outcome and a larger study may be able to identify other important parameters as well. A larger study may also enable us to predict radiological outcome more accurately from the 1-month neutrophil count.

Interpretation

In conclusion, we have demonstrated that the blood neutrophil count after one month of therapy for tuberculosis strongly predicts poor radiological outcome, even after controlling for baseline severity. Future therapeutic strategies to mitigate this risk should include rapid control of mycobacterial replication (and thereby the associated inflammation) in patients presenting with neutrophilia – for example, via the use of additional anti-tuberculous drugs. Host-directed therapies to reduce neutrophil-mediated lung damage should also be urgently investigated, as they offer a potential approach to management in people identified at month 1 of treatment as being at greatest risk of long-term lung damage. Recent trials targeting neutrophils in bronchiectasis with agents such as brensocatib have been encouraging [34] and offer hope that severe post-tuberculous lung disease is not inevitable.

Authors' Contributions: DML and MCIL conceived the study. TPWJ, SD and IM extracted data. JC and CC scored chest x-rays. TPWJ and DML performed analysis. TPWJ, MCIL and DML drafted the manuscript. All authors reviewed the manuscript, and all read and approved the final version. DML is the guarantor of the data.

Take-Home Point

Study Question: What are the predictors of radiological severity at the end of treatment for tuberculosis?

Results: The only significant predictor of radiological severity at the end of treatment was the neutrophil count after one month of anti-tuberculosis therapy.

Interpretation: Persistent neutrophilic inflammation on treatment associates with poor radiological outcome and may be a target for intervention.

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Figure Legends

Figure 1. A. Total radiological severity (Ralph) score at baseline, 2 months of treatment and end of treatment. B. Change in Ralph score from baseline to 2 months and end of treatment. C. Proportion of lung affected at each time point. D. Largest cavity size at each time point among patients with cavities identified on baseline x-rays. E. Neutrophil count at baseline and after 1 month of treatment. F. C-Reactive protein (CRP) at baseline and after 1 month of treatment. N=154 patients (A, B, C, E), 55 patients (D), 150 patients (F).

Figure 2. Proportions of patients with (A) pleural thickening, (B) cavitation, (C) fibrosis, (D) volume loss and (E) effusion at baseline (n=154), after 2 months of treatment (n=129) and at end of treatment (n=144). For pleural thickening, fibrosis and volume loss, results are presented as definite if both radiologists recorded this feature or indeterminate if only one radiologist recorded it. For cavitation and effusion, results are presented according to size as per the associated legends.

Figure 3. A. Neutrophil count after 1 month of treatment in patients with cavities identified ('Cavity') or not identified ('No cavity') at the end of treatment (n=139). B. Neutrophil count after 1 month of treatment in patients with pleural effusions identified ('Effusion') or not identified ('No effusion') at the end of treatment (n=130). C. Neutrophil count after 1 month of treatment in patients who had cavities identified at baseline and who either still had cavities at end of treatment ('Persisted') or who did not have cavities identified at end of treatment ('Resolved') (n=52). D. Neutrophil count after 1 month of treatment in patients who had pleural effusions identified at baseline and who either still had effusions at end of treatment ('Persisted') or who did not have effusions identified at end of treatment ('Resolved') (n=31).

Table 1. Baseline demographics and clinical parameters

Age, years (Mean ± SD)	37 ± 16
Sex (n, % female)	57 (37.0%)
Ethnicity*	
White (n, %)	30 (19.5%)
South Asian (n, %)	45 (29.2%)
Black (n, %)	46 (29.9%)
Other (n, %)	27 (17.5%)
Not recorded (n, %)	6 (3.9%)
Smoking	
Current smoker (n, %)	21 (13.6%)
Ex-smoker (n, %)	17 (11.0%)
Non-smoker (n, %)	43 (27.9%)
Not recorded (n, %)	73 (47.4%)
Duration of symptoms prior to starting treatment, days (median [IQR]; n=125)	44 [27-84]
Sputum smear positivity	
Negative (n, %)	91 (59.1%)
Positive (n, %)	48 (30.8%)
1+	19
2+	14
3+	10
4+	2
Not recorded	3
Not done / not recorded (n, %)	15 (9.7%)
Cavities present on baseline chest x-ray	55 (35.7%)
Time to culture positivity, days (Mean ± SD)	13 ± 10
Days to 1-month blood test (median [IQR])	31 [22-40]
Days to 2-month chest x-ray (median [IQR])	61 [53-70]

* South Asian – Indian, Pakistani, Bangladeshi, Nepalese; Black includes Black African and Black Caribbean

SD, standard deviation; IQR, interquartile range

Table 2. Correlates of Baseline CXR Ralph score

	Univariate	p value	Multivariate p value
Age	r= 0.19	**0.019**	0.13
Sex			
Male	Mean 34.9	0.64	
Female	Mean 37.5		
Ethnicity			
White	Mean 52.5	**0.030**	0.76
South Asian	Mean 29.9		
Black	Mean 36.0		
Other	Mean 31.1		
Not recorded	Mean 16.7		
Smoking			
Current smoker	Mean 40.5	0.69	
Ex-smoker	Mean 34.7		
Non-smoker	Mean 30.8		
Not recorded	Mean 37.7		
Duration of symptoms prior to starting treatment	ρ= 0.003	0.97	
Sputum smear grade	Mean 25.9	**<0.001**	**0.003**
0	Mean 61.1		
1+	Mean 61.4		
2+	Mean 69.5		
3+	Mean 102.5		
4+			
Time to culture positivity	r= -0.16	0.08	0.98
Baseline neutrophil count	r= 0.26	**0.001**	**<0.001**
Baseline CRP	r= 0.21	**0.011**	0.45

CRP, C-reactive protein

Table 3. Correlates of 2-month CXR Ralph score

	Univariate	p value	Multivariate p value
Age	r= 0.32	**<0.001**	0.07
Sex			
Male	Mean 26.6	0.69	
Female	Mean 24.3		
Ethnicity			
White	Mean 37.6	0.10	0.82
South Asian	Mean 29.3		
Black	Mean 23.2		
Other	Mean 16.7		
Not recorded	Mean 7.0		
Smoking			
Current smoker	Mean 25.3	0.89	
Ex-smoker	Mean 21.9		
Non-smoker	Mean 24.0		
Not recorded	Mean 27.8		
Duration of symptoms prior to starting treatment	ρ= -0.03	0.77	
Sputum smear grade			
0	Mean 14.9	**<0.001**	**0.001**
1+	Mean 31.1		
2+	Mean 53.3		
3+	Mean 64.5		
4+	Mean 110.0		
Time to culture positivity	r= -0.19	0.057	0.39
Baseline neutrophil count	r= 0.22	**0.012**	0.47
Baseline CRP	r= 0.34	**<0.001**	0.21
1-month neutrophil count	r= 0.54	**<0.001**	**<0.001**
1-month CRP	r= 0.49	**<0.001**	0.79

CRP, C-reactive protein

Table 4. Correlates of 6-month CXR Ralph score

	Univariate	**p value**	**Multivariate p value**	**Multivariate p value including baseline Ralph score**
Age	r= 0.23	**0.006**	0.49	0.50
Sex **Male** **Female**	 Mean 11.7 Mean 13.4	 0.65		
Ethnicity **White** **South Asian** **Black** **Other** **Not recorded**	 Mean 19.0 Mean 14.2 Mean 11.4 Mean 4.6 Mean 5.0	 0.072	0.45	0.53
Smoking **Current smoker** **Ex-smoker** **Non-smoker** **Not recorded**	 Mean 20.2 Mean 8.2 Mean 10.9 Mean 11.7	 0.22		
Duration of symptoms prior to starting treatment	ρ= 0.03	0.79		
Sputum smear grade **0** **1+** **2+** **3+** **4+**	 Mean 9.0 Mean 10.3 Mean 28.5 Mean 24.5 Mean 47.5	 **<0.001**	0.11	0.28
Time to culture positivity	r= -0.20	**0.037**	0.18	0.28
Baseline neutrophil count	r= 0.13	0.14		
Baseline CRP	r= 0.09	0.30		
1-month neutrophil count	r= 0.34	**<0.001**	**0.003**	**0.01**
1-month CRP	r= 0.29	**0.001**	0.79	0.62
Baseline Ralph score	R= 0.42	**<0.001**		0.14

CRP, C-reactive protein

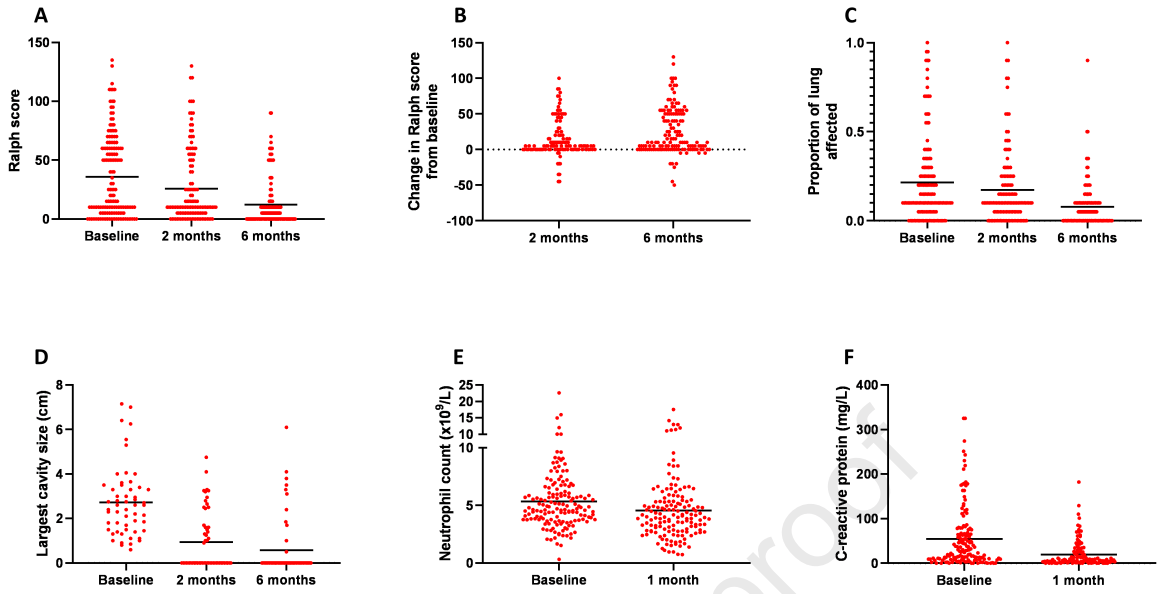
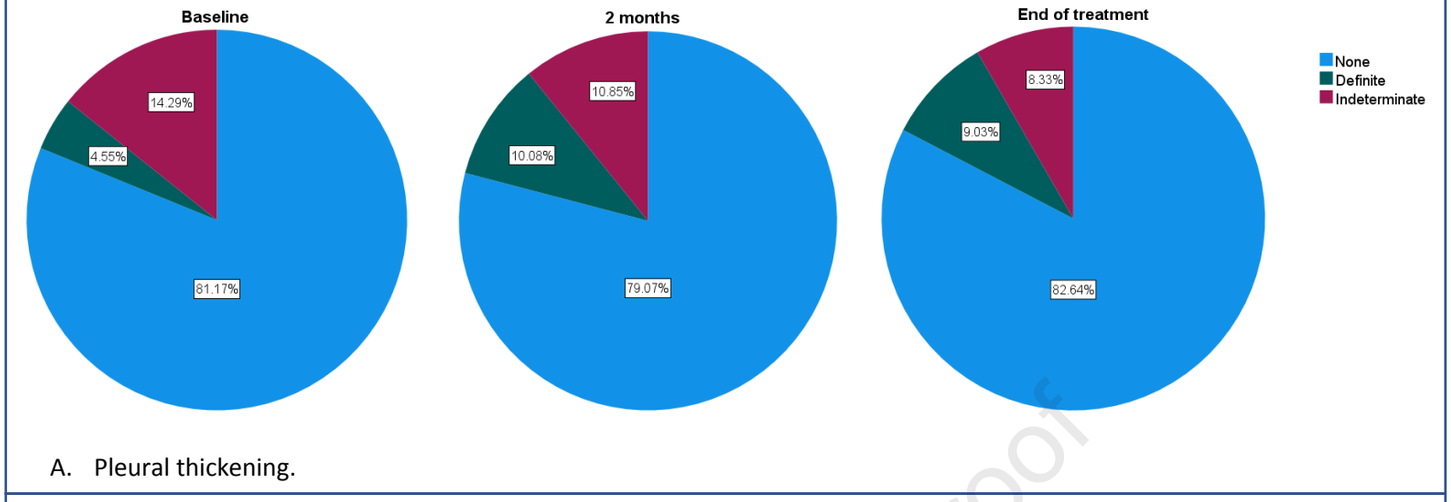
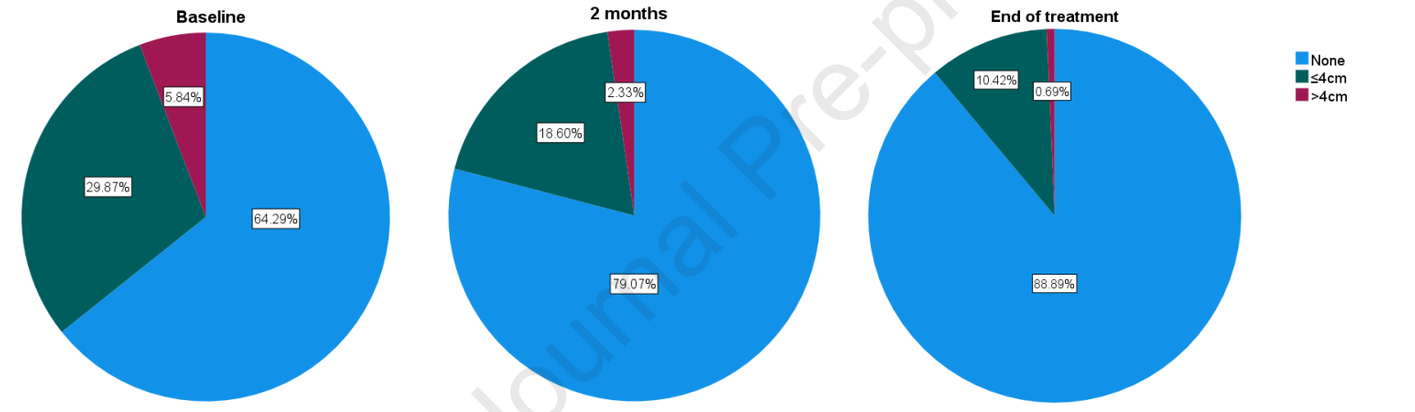


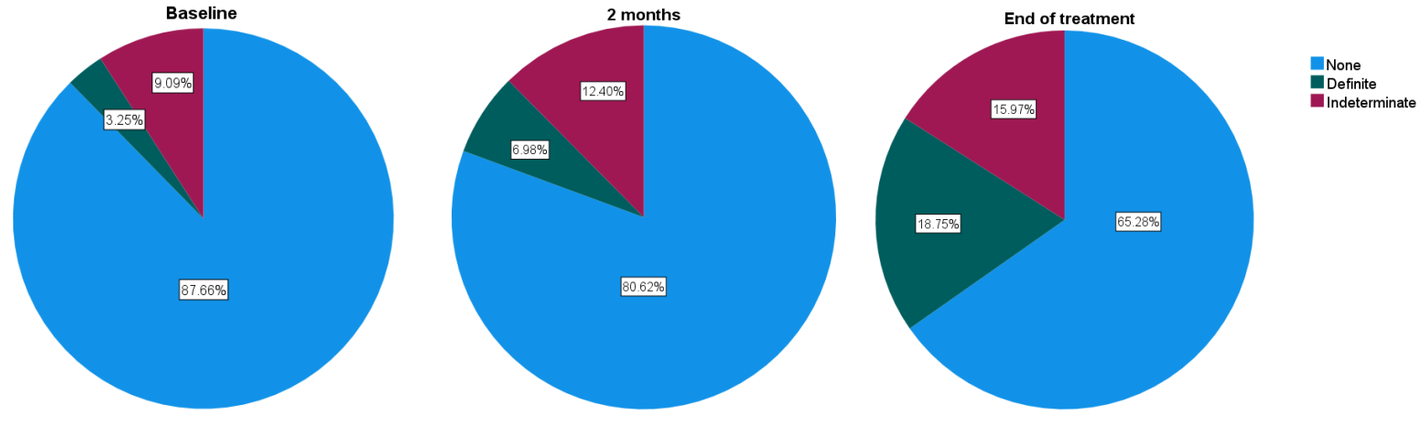
Figure 1



A. Pleural thickening.



B. Cavitation.



C. Fibrosis.

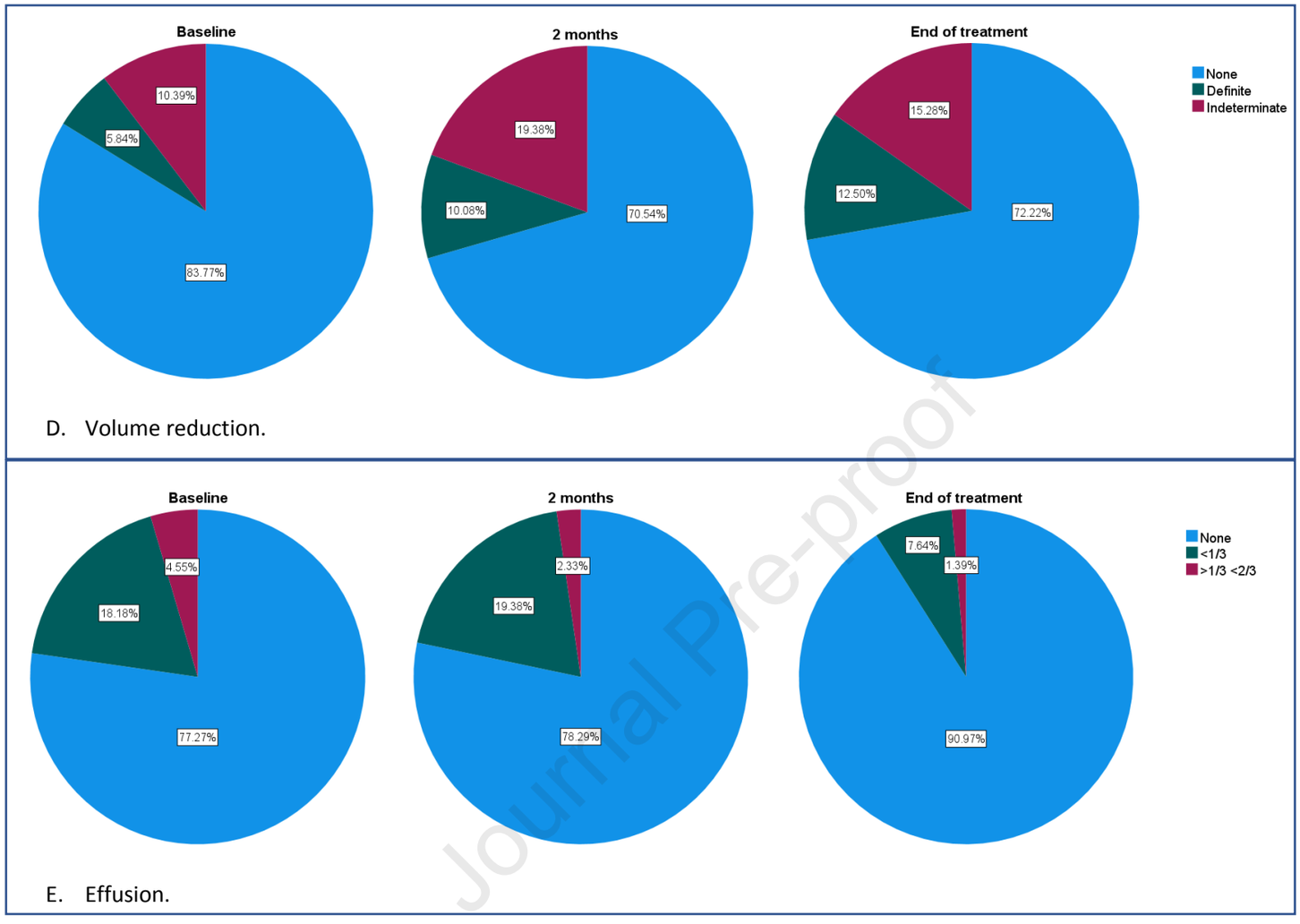


Figure 2. Proportions of patients with (A) pleural thickening, (B) cavitation, (C) fibrosis, (D) volume loss and (E) effusion at baseline, after 2 months of treatment and at end of treatment. For pleural thickening, fibrosis and volume loss, results are presented as definite if both radiologists recorded this feature or indeterminate if only one radiologist recorded it. For cavitation and effusion, results are presented according to size as per the associated legends.

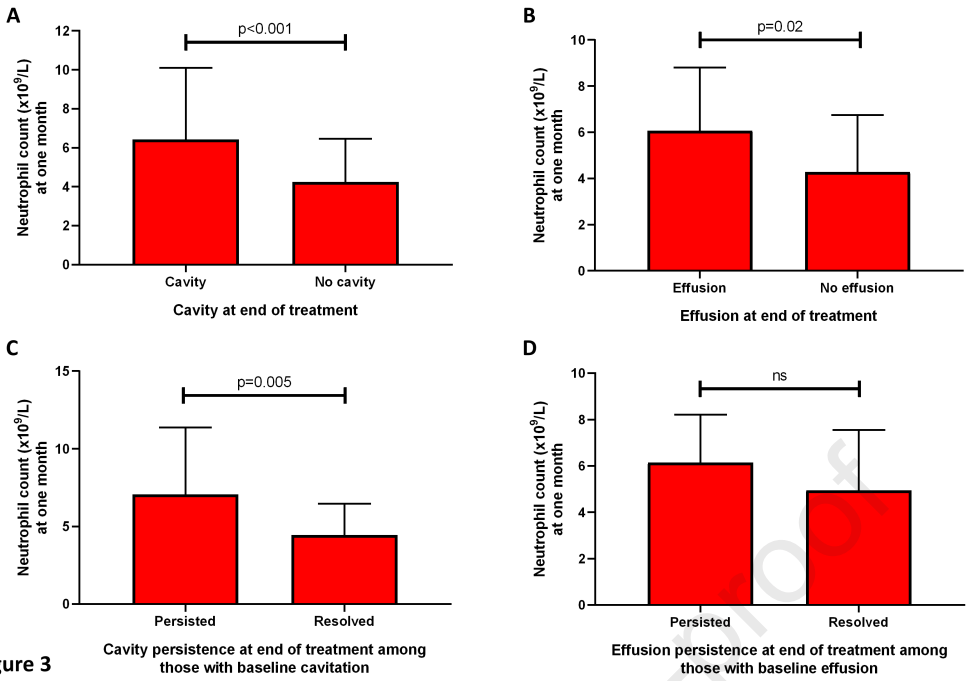


Figure 3