Section: Respiratory Medicine

Original Research Article

TO STUDY THE INFLAMMATORY MARKERS IN ACTIVE PULMONARY TUBERCULOSIS, ITS CORRELATION WITH DISEASE SEVERITY, AND ITS RESPONSE TO ANTI-TUBERCULAR TREATMENT

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Abstract

Background: Tuberculosis is thought to be one of the oldest human diseases; the history of TB is at least as old as humankind over the years. **Aim:** The study aims to prove that inflammatory marker levels reflect the disease severity and its decline reflects a response to treatment. **Materials and Methods:** A prospective cross-sectional study was conducted at three tertiary care institutes for 6 months. A total of 101 patients attending the thoracic medicine outpatient clinic in the government Thiruvotteswarar hospital of thoracic medicine (GTHTM) and government Kilpauk Medical College (KMC), Government Royapettah Hospital (GRH), with newly detected sputum positive pulmonary tuberculosis. Informed consent was obtained from all patients before the study started. Patients with new sputum-positive pulmonary tuberculosis and age >18 < 70 years were included. **Result:** In our study, males accounted for 74%, and females accounted for 25%. The mean age distribution is 40 years, with a maximum of 70 and a minimum of 18 years. The mean CRP is slightly higher in men both before and after treatment. The mean values of CRP, ESR, NLR, and RDW fall significantly after treatment for 2 months in both males and females. There was a significant difference in CRP, ESR, NLR, and RDW Sputum categories between treatments. **Conclusion:** The findings of our study can be extrapolated and useful in assessing the disease severity and follow-up in pediatric and extrapulmonary TB, where sampling from the primary site is not always possible, or correlation with other modalities of investigation is questionable.

INTRODUCTION

Tuberculosis is thought to be one of the oldest human diseases; the history of TB is at least as old as humankind over the years. Not only the medical implications but also the social and economic impact of TB has been a major cause of suffering and death since immemorial.[1] At the dawn of the new millennium, we are still mute witnesses to the silent yet efficient march of this sagacious disease, its myriad manifestations and its unequalled, vicious killing power through the millennia. TB never disappeared from the developing world. The most technologically advanced world has seen more than a century of declining incidence of tuberculosis. Still, the less developed world has not been so fortunate, and in those populous regions, TB incidence is increasing. In acquired immunodeficiency region (AIDS) stricken regions – sub–Saharan Africa, for example –TB case rates now are 50-100 times those in North America and Europe.[2]

Spurred by immune deficiencies resulting from HIV infection, these case rates will continue to increase in the coming decades. The history of tuberculosis reveals that this disease has swept across large regions of the world in slowly moving epidemic waves with periods measured in centuries. The factors contributing to the rise and decline of these waves are only partially known and are difficult to control in the absence of massive political changes.

However, we might learn from considering the historical spread of TB and the ways those countries now favoured with low TB incidences managed their high incidence problems in their region.[3]

Patients with pulmonary tuberculosis depend on monitoring sputum smear/culture-based treatment. But this will be challenging to use in extrapulmonary TB and patients with paucibacillary disease, such as HIV-coinfected patients and children. Furthermore, both sputum volume and quality decrease in response to treatment and many patients cannot provide sputum samples for culture/smear after a few weeks of treatment. The development of non-sputum-based biomarkers of treatment response would represent an advance for individual monitoring of TB patients.[4]

Hence, we proposed that these inflammatory markers will be an indispensable tool in assessing tuberculosis disease severity, and their fall in response to treatment will be surrogate markers of disease control. Therefore, we selected the inflammatory marker C-reactive protein, ESR, NLR, and RDW in our study and proceeded.

Aim

To prove that inflammatory marker levels reflect the disease severity and its decline reflects a response to treatment, thus these inflammatory markers can be used as an adjunct in microbiologically confirmed TB cases and as a prime tool in clinically diagnosed cases.

MATERIALS AND METHODS

A prospective cross-sectional study was conducted at three tertiary care institutes for 6 months. A total of 101 patients attending the thoracic medicine outpatient clinic in the government Thiruvotteswarar hospital of thoracic medicine (GTHTM) and government Kilpauk Medical College (KMC), Government Royapettah Hospital (GRH), with newly detected sputum positive pulmonary tuberculosis. Informed consent was obtained from all patients before the study started. Patients with new sputum-positive pulmonary tuberculosis and age >18 < 70 years were included.

Patients with the following co-morbidities, previous anti-tubercular treatment, COPD, bronchial asthma, ischemic heart disease, decompensated liver disease, diabetes mellitus, renal failure, peripheral vascular disease, HIV, Collagen vascular disease & patients on chronic drugs were excluded.

Symptoms of pulmonary tuberculosis are suspected of fever, weight loss, significant weight loss, hemoptysis, and any abnormalities in the chest radiograph as per technical operational guidelines 2016. Such patients suspected of pulmonary tuberculosis were screened with sputum smear examination for acid-fast bacilli and new sputum-positive patients of pulmonary tuberculosis who are not taken anti-tuberculous treatment before being selected for the study

Smears can be graded according to the number of bacilli seen. In addition, many chest x-ray scores are available for adults to predict the outcome and correlate with bacteriological and clinical severity markers. The scoring systems assess the extent of involvement of lung fields, percentage of lung involvement, presence of cavities, pleural effusion etc.

Pearson correlation is used to assess the strength of correlation between variables. Next, the chi-square test is performed between two groups, and its statistical significance is calculated. Finally, the chi-square ($\chi 2$) test of independence is used to test for a statistically significant relationship between two categorical variables.

RESULTS

Table 1: Demographic data of the study

		Frequency (%)
Gender	Male	75 (74.3%)
	Female	26 (25.7%)
Sputum category	1+	39 (38.6%)
	2+	14 (13.9%)
	3+	34 (33.7%)
	Scanty	14 (13.9%)
Category	Mild	30 (29.7%)
	Moderate	27 (26.7%)
	Severe	44 (43.6%)

In our study, males accounted for 74%, and females accounted for 25%. The mean age distribution is 40 years, with a maximum of 70 and a minimum of 18 years. Mild disease with 1+ sputum predominated at 38.6%, followed by sputum 3+ at about 33%, and scanty and 2+ and scanty accounted for 14% each. According to radiological grading, the people with mild, moderate, and severe diseases are 30%, 27%, and 44% [Table 1].

Table 2: Comparison of sputum category and severity between gender

		Gender		P-value
		Male	Female	
Sputum category	1+	34	19	<0.0001
	2+	7	7	

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	3+	34	0	
Severity	1	16	14	<0.0001
	2	18	9	
	3	41	3	

The males were more in number in mild disease and severe disease. Males and females are equal in number in moderate disease. In a severe disease that is with 3+ sputum, there were no females. In mild disease, males and females are almost equal (16) and (14). In moderate disease, males predominated (18) compared to females (9). In severe disease, males were dominant (41), but only a few females (3) [Table 2].

Table 3: Comparison of gender and severity between treatments

			Before Rx	After Rx	P-value
CRP	Gender	Male	58.4 ± 29.8	23.5 ± 15.3	0.001
		Female	28.6 ± 23.4	7.8 ± 10.2	
	Severity	Mild	21.04 ± 12.8	4.7 ± 4.8	0.047
		Moderate	43.3 ± 11.0	18.1 ± 10.7	0.013
		Severe	75.61 ± 28	30.6 ± 14.5	0.001
ESR	Gender	Male	54.6 ± 24.5	31.6 ± 7.39	0.756
		Female	41.8 ± 10.07	26.85 ± 5.17	
	Severity	Mild	37.1 ± 8.04	27.63 ± 5.96	0.66
		Moderate	41.6 ± 8.2	27 ± 3.5	0.04
		Severe	67.0 ± 25.2	34.3 ± 7.7	0.001
NLR	Gender	Male	6.06 ± 2.3	3.79 ± 1.2	0.004
		Female	4.19 ± 1.27	3.23 ± 0.56	
	Severity	Mild	3.8 ± 0.59	3.16 ± 0.48	0.006
		Moderate	4.6 ± 1.2	3.5 ± 0.64	0.535
		Severe	7.39 ± 2.2	4.07 ± 1.51	0.105
RDW	Gender	Male	14.8 ± 1.5	13.8 ± 0.98	0.044
		Female	15.3 ± 1.7	13.5 ± 0.72	
	Severity	Mild	14.4 ± 1.3	13.2 ± 0.52	0.15
		Moderate	14.8 ± 1.5	13.8 ± 0.83	0.05
		Severe	15.3 ± 1.6	14.04 ± 1.06	0.04

The mean CRP is slightly higher in men both before and after treatment. Comparing the mean value of CRP and ESR, their levels are higher and higher in severe, moderate, and mild diseases. Thus, their mean levels closely reflect the severity. (radiology) and (by sputum category). The mean values of CRP, ESR, NLR, and RDW fall significantly after treatment for 2 months in both males and females.
There was a significant difference between treatments in CRP severity; mild, moderate, and severe. There was a significant difference between treatments in ESR and RDW severity; moderate and severe. There was a significant difference between treatments in NLR severity (Mild) [Table 3].

Table 4: Haematological parameters before and after treatments

		Before Rx	**After Rx**	**P-value**
CRP	1+	33.32 ± 20.8	11.06 ± 11.91	0.001
	2+	57.9 ± 30.4	21.2 ± 15.3	0.001
	3+	75.0 ± 27.7	32 ± 12	0.001
ESR	1+	42.6 ± 17.4	28.4 ± 5.42	0.001
	2+	52.2 ± 14.3	30.3 ± 6.04	0.032
	3+	64.5 ± 25.8	33.4 ± 8.8	0.001
NLR	1+	4.5 ± 1.4	3.3 ± 0.69	0.001
	2+	6.09 ± 2.4	3.7 ± 0.70	0.001
	3+	6.9 ± 2.66	4 ± 1.66	0.186
RDW	1+	14.9 ± 1.68	13.5 ± 0.76	0.001
	2+	15 ± 1.81	14.3 ± 1.77	0.268
	3+	14.8 ± 1.3	13.8 ± 0.53	0.03

There was a significant difference in CRP and ESR Sputum categories; 1+, 2+, and 3+ between treatments. There was a significant difference between treatments in the NLR Sputum category, 1+ and 2+, but no significant difference in 3+. There was a significant difference in the RDW Sputum category: 1+ and 3+ between treatments, but no significant difference in 2+ [Table 4].

DISCUSSION

In our study population, male patients accounted for about 75%, and female patients accounted for about 25%. Thus, males predominated in the study. This probably shows men seek medical care more than women. The mean age of the patients is 40 years, with a standard deviation of.[11] The maximum age of the patient was 70 years, and the minimum was 18 years. This reflects that TB predominantly affects the productive age group, a major socioeconomic burden for the country. In this study, 53% of the patients had

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mild, 14 % had a moderate category, and 34% were in a severe category. Thus, mild disease predominated, reflecting the integrity of the health system and people's awareness. According to gender, males predominated in mild and severe diseases, and in moderate diseases, it is in an equal distribution. No female patients classified as having severe disease may probably be due to the relatively less female study population. According to radiology, 30% of patients are classified into mild disease, 27% into moderate disease, and 44% severe. Thus, there is a discrepancy in classifying the severity between the sputum category and radiology.

The radiological evaluation detected more Moderate diseases as compared to sputum grading. Although according to gender, male and female distribution in mild disease is almost equal, in moderate and severe disease, males predominated. Thus, males suffer relatively severe diseases. The levels of inflammatory markers (CRP, ESR, NLR, and RDW) were higher in mild and moderate disease cases classified by the sputum category compared to the radiology category. This suggests that the sputum category may better indicate disease severity in mild and moderate cases of PTB. The levels of inflammatory markers (CRP, ESR, NLR, and RDW) were similar in severe disease cases classified by sputum category and radiology category, except for RDW, which was higher in severe disease cases determined by radiology. This suggests that the radiology category may better indicate disease severity in severe cases of PTB for RDW.

The CRP levels, elevated during active disease, decrease significantly after 2 months of ATT in mild, moderate and severe disease with p-value < 0.001. The following previous studies by Abakay et al.5 found that patients with advanced PTB had higher RDW values (17.7% versus 15.7%, p=0.002) and NLR values (4.7 versus 3.1, p=0.009) compared to patients with mild to moderate PTB.

Furuhashi et al.[6] reported that CRP values had a significant correlation with the sputum smear scale and the degree of lung lesions and were found to be elevated in patients with bilateral lung involvement. Dar et al.[7] found that treatment with ATT significantly decreased CRP and IFN-γ levels in PTB patients, with CRP levels decreasing from 7.7 mg/dl to 2.41 mg/dl and IFN-γ levels decreasing from 12.53 pg/ml to 2.47 pg/ml for 6 months.

In our study, the ESR, elevated in active disease, falls significantly in moderate and severe disease (p-value < 0.001). In contrast, its fall in mild disease is not statistically significant (p-value 0.66). Furthermore, a study by Babu et al.8 found that the hs-CRP levels of metabolic syndrome and severe metabolic syndrome groups in males were significantly higher than in the control group (P<0.001). But there was no significant difference in hs-CRP levels in the female group (P=0.156).

The NLR ratio was elevated in active disease and significantly in mild disease (p < 0.006), whereas in moderate and severe disease fall in its level was not significant (p=0.5). This follows various literature examples studies that concluded high NLR in severe disease and retreatment cases. Abakay et al.[5] proposed that NLR and RDW could be used as markers of inflammation to aid in the clinical management of TB patients and to evaluate the degree of the disease. Yin et al.[9] found that having an NLR of ≥ 2.53 is a predictor of PTB retreatment, in addition to other risk factors such as initial cavitation on chest X-ray, history of smoking, and age of ≥ 60.

The red cell distribution width (RDW) levels that are elevated in active disease fall in response to the active treatment but are not statistically significant. Studies done by Miranda et al.[10] found that measuring CRP and Ferritin levels in the blood may be useful in identifying patients with positive TB cultures after 60 days of Anti-Tuberculosis Treatment (ATT). This can assist in the early detection of treatment failure and in initiating appropriate management strategies. However, CRP is a better marker indicating disease severity and prognosis, followed by ESR. Though the RDW and NLR were good markers of disease severity, they are unreliable in assessing the disease prognosis and need further study to prove their usefulness.

CONCLUSION

The findings of our study can be extrapolated and useful in assessing the disease severity and follow-up in pediatric and extrapulmonary TB, where sampling from the primary site is not always possible, or correlation with other modalities of investigation is questionable. Thus, developing non-sputum-based biomarkers of treatment response would represent an advance for individual monitoring of TB patients.

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