Original Article

Hematological Parameters in Patients with Pulmonary Tuberculosis and its Presentation among Favorable and Unfavorable Treatment Outcomes

S. Ramesh Kumar[1], Chandrasekaran Kandhasamy[2], V. Banurekha Velayutham[3], Ponnuraja Chinnaiyan[4], Muthuramalingam Kannan[5], M. S. Jawahar[6], C. Padmapriyadarsini[7]

[1]Scientist F (Medical), [2]Principal Technical Officer, ICMR-National Institute for Research in Tuberculosis, Madurai Unit, Madurai, [3]Scientist E (Medical), [4]Scientist E, [5]Technical Officer A, [6]Former Scientist G (Medical), [7]Scientist G and Director, ICMR-National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India

Abstract

Background: Tuberculosis (TB) management continues to be a challenge globally; weakened immunity plays a significant role in the reactivation of TB. There is limited information on hematological parameters in patients with pulmonary TB and its association with outcome. **Objectives:** We present hematological parameters of newly diagnosed sputum-positive pulmonary TB patients enrolled in a randomized, clinical trial that assessed the efficacy and safety of 3 and 4 regimens using moxifloxacin. **Materials and Methods:** Blood hematological parameters at baseline, comparison of the baseline and end of treatment values, including the monocytes by lymphocytes ratio (M/L), neutrophil lymphocyte ratio (N/L), and platelet lymphocyte ratio (P/L) between the patients with favorable and unfavorable TB treatment outcome, and among different age group and sex presented in this paper. **Results:** Among the total 1059 patients, 782 were males, the mean hemoglobin (HB) ± standard deviation (SD) was 11.5 g/dL ± 2.0, the mean white blood cell (WBC) count ± SD was 9800 ± 3009 and the mean platelet count (in lakhs) ± SD was 4.24 ± 1.42 cells/uL. There was an increase from baseline in the mean hemoglobin, eosinophil, and lymphocyte count and a decrease in mean neutrophil, monocyte counts to the end of treatment. There was a decrease in baseline mean total WBC count posttreatment, both in favorable (10,271 cells/uL ± 3007 SD to 6689 cells/uL ± 1837 SD, [$P \leq 0.001$]), and unfavorable TB outcome patients. **Conclusion:** An increase in HB, and a decrease in WBC count, M/L, N/L, and P/L ratio is possible at the end of TB treatment and future studies to correlate blood hematology parameters with TB treatment outcome.

Key words: Clinical trial, hematology, hemoglobin, outcome, pulmonary tuberculosis, white blood cell count

Introduction

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and the leading cause of a single infectious agent (above HIV/AIDS). As per the WHO TB Report 2021, globally, in 2020, there were an estimated 1.3 million (95% uncertainty interval [UI]: 1.2–1.4 million) deaths among HIV-negative people, up from 1.2 million (UI: 1.1–1.3 million) in 2019.[1] Weakened immunity plays a significant role in the reactivation of TB. There has been limited information on the hematological parameters in patients with pulmonary TB. Commonly encountered hematological changes in acquiring TB disease include anemia, raised erythrocyte sedimentation rate, leukopenia, neutropenia, lymphocytopenia, monocytopenia, leukocytosis, neutrophilia, lymphocytosis, monocytosis, and thrombocytopenia.[2-4] It has been shown that the ratio of monocytes to lymphocytes <9% or >25% is predictive of active TB.[5] There is limited information on studies on hematological parameters and TB outcomes.[4] Blood hematology, being a simple test that is routinely done, could give a clue to the management of TB. With a high TB burden in a country like India, understanding the various dimensions of TB aspects is

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Address for correspondence: Dr. S. Ramesh Kumar, ICMR-NIRT Madurai Unit, Ward 62 (Upstairs), Government Rajaji Hospital, Madurai - 625 020, Tamil Nadu, India.
E-mail: ramesh@nirt.res.in

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important for containing the TB spread. Understanding the immunity part by simple hematology testing in the management of TB is important. We analyzed the hematological parameters of the pulmonary TB patients started on anti tuberculous therapy and the changes in the parameters between those who had favorable and unfavorable TB outcomes in one of the clinical trials conducted at our center.

Materials and Methods

We conducted a randomized, open-label, parallel-arm, clinical trial to assess the efficacy and safety of three and four regimens using moxifloxacin in patients with newly diagnosed sputum-positive pulmonary TB. The study was approved by the NIRT Scientific Advisory Committee and Institutional Ethics Committee and is registered in the Clinical Trials Registry of India (CTRI 2008/091/000024). The study was conducted from 2007 to 2018. Study participants were newly diagnosed, adult, sputum-positive pulmonary TB patients consenting to investigations, daily supervised outpatient treatment, and home visits by study staff were enrolled at Chennai and Madurai. Informed consent was obtained from the patient before enrolment to the study. Treatment Regimens: eligible patients were randomly allocated in a 1:1:1:1:1 ratio to one of four test regimens or a control regimen as follows: Test regimen 1: Rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and moxifloxacin (M) daily for 3 months-3 RHZEM (M3); Test regimen 2: RHZEM daily for 2 months, followed by RHM daily for 2 months-2 RHZEM/2 RHM (M4); Test regimen 3: RHZEM daily for 2 months, followed by RHM thrice weekly for 2 months-2 RHZEM/2 RHM3 (M4-I); Test regimen 4: RHZEM daily for 2 months followed by RHEM thrice weekly for 2 months-2 RHZEM/2 RHEM3 (M4-IE); Control regimen: RHZE thrice-weekly for 2 months followed by RH thrice-weekly for 4 months-2 RHZE3/4RH3 (Control regimen) (C). The patients enrolled were subjected to blood investigations at baseline and follow-up months during TB treatment at 1st, 2nd, 3rd, 4th, and/or 6 months based on the study regimen allotted. The main study findings that included the efficacy analysis have been published.[6] The sample size calculation for the main clinical trial is as follows: using an equivalence design with a margin of indifference of 5%, and we assumed the efficacy of the control regimen to be 95% TB recurrence-free survival over 24 months posttreatment. With a type I error of 0.05 and a type II error of 0.20, the sample size was calculated to be 298 patients per regimen, and adjusting the 10% attrition rate, the final sample size was calculated to be 330 patients per regimen. Of 1371 patients, randomized, modified intention-to-treat analysis was done in 1329, and per-protocol analysis was done in 1223 patients. Regimen M3 was terminated due to high TB recurrence rates. The objective of this retrospective subanalysis was to assess the presentation of hematological parameters in new sputum-positive pulmonary TB patients and to assess the change in the hematological parameters in patients with favorable and unfavorable treatment outcomes. In this paper, we present the hematological parameters of the pulmonary TB patients enrolled in the clinical trial with information on blood hematology parameters available at baseline, including the end of treatment for the analysis. Blood hematology parameters included hemoglobin, total white blood cell (WBC) count, and differential count that included neutrophil, basophil, eosinophil, lymphocytes and monocytes count, and platelet count. We compared the blood hematological parameter values of those patients with the TB outcome and presented the results of the analysis in this paper. The TB outcome was defined as favorable if there was a cure and unfavorable if there was failure or relapse. We calculated the monocytes by lymphocytes ratio (M/L ratio), neutrophil by lymphocytes ratio (N/L ratio), and platelets by lymphocytes ratio (P/L ratio) at baseline and end of treatment for the patients and compared the same for both the favorable and unfavorable TB outcome patients.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), IBM, Chicago, IL, U.S.A, version 25 software. Descriptive statistics for demographic and blood parameters were done. We have compared the baseline and end-of-treatment values of blood parameters using paired samples *t*-test and used independent samples *t*-test for comparing the end of Rx blood parameters between treatment outcome, sex, and age groups.

Results

Of the total of 1059 patients with baseline hematological data available, the mean hemoglobin (HB) ± standard deviation (SD) was 11.5 g/dL ± 2.0, the mean WBC count ± SD was 9800 ± 3009 cells/uL, the mean red blood cell count (in lakhs) ± SD was 4.44 ± 0.58 cells/uL, and mean platelet count (in lakhs) ± SD was 4.24 ± 1.42 cells/uL. Among the total 1059 patients, 782 were male (74%) and 277 (26%) were female, about 50% were between 18 and 34 years (n = 527), 38% (n = 401) were between 30 and 50 years, and about 12% were more than 50 years old (n = 131). Regimen wise break up of baseline details of haematological parameters of TB patients enrolled for the study is presented in Table 1. There was a decrease in mean neutrophil, and monocyte counts from 67 to 53% (P = 0.01) and 9.5%–8.2% (P = 0.01), respectively, from baseline to end of treatment and there was an increase of mean eosinophil and lymphocytes count from 3.3% to 6.3% (P = 0.01) and 20%–32% (P = 0.01), respectively, post-TB treatment. The mean platelet count decreased from 4.37 ± 1.42 SD to 2.79 ± 0.95 SD lakhs per ml (P = 0.01). There was an increase from baseline mean hemoglobin count posttreatment, that was statistically significant and the increase was present in both favorable (11.5 g/dL ± 2.00 SD to 12.8 g/dL ± 2.04 SD [P = 0.01]) and unfavorable TB outcome patients (11.6 ± 2.4 SD to 12.6 ± 2.5 SD g/dL [P = 0.003]). Similarly, there was a decrease from baseline in the mean total WBC count posttreatment, both in favorable (10,271 cells/uL ± 3007 SD to 6689 cells/uL ± 1837 SD, [P = 0.01]), and unfavorable TB outcome patients (9675 cells/uL ± 2609 SD to

7642 cells/uL ± 2067 SD, [$P = 0.01$]), and that was statistically significant. There was also a decrease from baseline in the mean M/L ratio posttreatment, both in favorable (from 0.577 ± 0.92 SD to 0.330 ± 0.84 SD [$P = 0.01$]) and unfavorable TB outcome patients (from 0.563 ± 0.22 SD to 0.350 ± 0.19 SD [$P = 0.01$]) and that was statistically significant. The changes in the mean values of HB, total WBC count, M/L ratio, N/L ratio, and P/L ratio from the baseline to the end of treatment are presented in Table 2. The mean total WBC count was lower in the patients who had unfavorable TB outcomes, than those who had a favorable TB outcome but was not statistically significant $P = 0.253$. The mean values of the baseline neutrophil, monocyte, lymphocyte count, M/L ratio, N/L ratio, and P/L ratio were very similar between the patients who had favorable and unfavorable TB outcomes. The hematological presentations at baseline and after treatment were similar between the male and female sexes and between the different age groups.

Discussion

Our study showed that post-TB treatment, there was an increase in HB, a decrease in total WBC count and also a decrease from baseline in the mean M/L ratio, which was statistically significant, irrespective of the TB treatment outcomes. A similar result has been published from a study done in Romania,[4] with a decrease in WBC and M/L ratio, but a decrease in HB as well at the end of treatment. The decrease in the total WBC from baseline posttreatment may be because of the normalizing of the counts that were elevated due to *Mycobacterium tuberculosis* infection is attributed to elevated polymorph nuclear leukocytes and macrophages. The increased systemic inflammation due to the higher TB load at baseline could be the reason for increased total WBC count at baseline and subsequent reduction after TB treatment, be explained by the fact that higher TB load having increased systemic inflammation being studied earlier.[7] The increase in hemoglobin might be due to the reversal of suppression of erythropoiesis by the inflammatory mediators that had led to TB-associated anemia. A similar increase in hemoglobin post-TB treatment was found in other studies as well.[7]

There was no change in the hematological presentations at baseline and the changes after treatment between the male and female sexes and between the different age groups, though some studies have reported male sex with a higher M/L.[8] The ratios, namely M/L, N/L, and P/L ratio declined significantly after TB treatment, but the ratios were very similar in both the patients with favorable and unfavorable TB outcomes, both at baseline and at the end of treatment, unlike the study report from Romania,[4] wherein the significant decrease was observed only among those whose sputum culture turned negative at 2nd month. The ratios at the end of TB treatment are not available in that study report as they have been restricted to 2nd-month culture results from findings. These ratios have recently been gaining importance, and many studies have been done to assess using them as a biomarker of TB severity.[9-11] A study done in China has demonstrated that the ratio of monocytes to lymphocytes <9%

Table 1: Baseline details of hematological parameters of tuberculosis patients enrolled for the study, regimen wise

Regimen	Hb (g), mean±SD	TC (cells/mm³), median±SD	Differential count (% mean±SD)				
			N	M	E	B	L
3RHZEM[7]	11.5±1.9	9050±2877	70±8	9.4±2.2	2.4±2.9	0.5±0.7	16.7±6.3
2RHZEM[7]/2RHM[7]	11.6±2.0	10,000±3083	68±9	8.9±3.5	2.3±2.9	0.5±0.3	18.8±8.1
2RHZEM[7]/2RHM[3]	11.8±2.0	10,000±2844	68±9	8.6±4.0	2.2±3.6	0.5±0.4	19.0±7.3
2RHZEM[7]/2RHEM[3]	11.5±2.3	9900±2923	69±9	8.7±3.7	2.6±3.3	0.5±0.3	18.0±7.4
2RHEZ[3]/4RH[3]	11.3±1.9	9700±3282	68±9	9.2±3.9	2.3±3.3	0.5±0.4	19.0±7.0

Duration of regimen in months is mentioned before the regimen in the intensive phase and continuation phase and drugs given daily or thrice weekly is mentioned in superscript as 7 or 3, respectively. R: Rifampicin, H: INH, Z: Pyrazinamide, E: Ethambutol, M: Moxifloxacin, SD: Standard deviation, TC: Total count

Table 2: Comparison of the changes in the hematological parameters of tuberculosis patients enrolled for the study, before and after the tuberculosis treatment among those who had favorable tuberculosis outcomes and among those who had unfavorable tuberculosis outcomes

Outcome	Hb (g/dL), mean count±SD			TC (cells/uL), median count±SD			M/L ratio, mean±SD		
	Baseline	End of RX	*P*	Baseline	End of RX	*P*	Baseline	End of RX	*P*
Favorable	11.52±2.00	12.76±2.04	<0.001	10271±3006	6690±1837	<0.001	0.577±0.92	0.330±0.84	<0.001
Unfavorable	11.55±2.40	12.55±2.49	<0.003	9675±2609	7643±2067	<0.001	0.563±0.22	0.350±0.19	<0.001

Outcome	N/L ratio, mean±SD			P/L ratio, mean±SD		
	Baseline	End of RX	*P*	Baseline	End of RX	*P*
Favorable	4.19±2.23	1.90±0.94	<0.001	0.26±0.15	0.096±0.05	<0.001
Unfavorable	4.18±2.45	2.59±1.30	<0.001	0.26±0.17	0.12±0.05	<0.001

SD: Standard deviation, M/L: Monocytes/Lymphocytes, N/L: Neutrophil/Lymphocyte, P/L: Platelet/lymphocyte, Hb: Hemoglobin, TC: Total count

or >25% is a predictive value of active TB. Furthermore, work up on these ratios, and utilizing its use in predicting the TB outcome has to be taken up in future studies. The role of platelet cells in inflammatory reactions in TB[12,13] and the occurrence of platelet-monocyte aggregation (PMA) in TB infection has been studied,[13] and it has been found that increased PMA may not be caused by platelets but by monocyte activation. We found a decrease in the median platelet count from 4.37 lakhs to 1.42 count lakhs among those patients treated. We hypothesise that there would have been a possibility of anti-TB drugs causing a low platelet count, but the level of the drop could have been mild and subclinical, as clinically significant thrombocytopenia did not appear in our cohort of patients.

It has been reported that increased neutrophil count before initiating TB treatment was associated with unfavorable treatment outcomes,[14] but we could not demonstrate any of the parameters, namely, total count, neutrophil, monocyte, and lymphocyte or any other count with TB outcome. We did find a difference in the total WBC count between favorable and unfavorable TB outcomes but was not statistically significant. We recommend more studies to assess the blood parameters with TB outcomes in future.

Public health significance

Blood hematology is a simple test that can indicate if the patient is responding to treatment as the parameters would mirror the reduction in infection status. Although microbiological status in sputum-positive pulmonary TB indicates treatment response, other tests which include hematology can provide an early indication of response to treatment and this needs further evaluation.

Conclusion

An increase in HB, a decrease in Total WBC count, and a decrease in M/L, N/L, and P/L ratio is possible at the end of TB treatment. Our study could not demonstrate the relationship of the blood hematology parameters with TB treatment outcome, as the comparison of the hematological parameters between favorable and unfavorable TB outcome groups did not get statistically significant differences, suggesting future studies to explore this.

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Conflicts of interest

There are no conflicts of interest.

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