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Original Article

# Hematological Profiles in Adult patients with Typhoid Fever — A comparative Cross-Sectional Study

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***ABSTRACT***

***Introduction:*** *Typhoid fever is among the leading causes of morbidity and mortality worldwide. The incidence is higher in developing countries. Changes in hematological profiles, among others, share a significant contribution to the morbidity and mortality from typhoid fever. Though studies have been conducted in developed countries, no published data is available in resource-constrained settings such as Ethiopia.* ***Objective:*** *To determine hematological profiles of adult patients with typhoid fever at Dilla University General Hospital, South Ethiopia.* ***Methods & Materials:*** *A comparative cross-sectional study was conducted on 174 participants using convenient sampling techniques. Clinical data were obtained from medical records and laboratory screening. CBC was made using the ADVIA 560 Hematology analyzer. Data was analyzed by SPSS (version 27, USA). An independent t-test and Mann-Whitney U-test were used for parametric and non-parametric data.* ***Result:*** *In this study, 55% of the participants were males. Almost half (47%) of the participants were in the age group of 29-41 years. There were no significant age differences among study groups. Hematological parameters, such as mean WBC, neutrophil, RBC, hemoglobin, hematocrit and platelet counts were found to be low in adult patients with typhoid fever compared to apparently healthy typhoid negative adults.* ***Conclusion:*** *Significant changes were reported in WBC, neutrophils, RBC, Hgb, HCT, and platelet count among typhoid fever patients. Routine hematological examinations, such as a complete blood count, are recommended for typhoid fever patients.*

***Keywords:*** *Hematological profiles, typhoid fever, Ethiopia*

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## INTRODUCTION

Typhoid fever, a systemic infection that poses multisystem clinical presentation, is caused by the bacterium *Salmonella typhi*, and occasionally by *Salmonella Paratyphi*. Transmission is feco-oral, often when contaminated food or water is consumed[1]. The disease has an incubation period of three to sixty days or more, on average, 8-14 days depending on the inoculums taken, and disease-fighting ability of individuals[2].

Globally, 14.3 million cases of typhoid fever are reported in 2022. About 10.3 million (71.8%) cases are in South Asia, while Southeast Asia, East Asia, and Oceania super-region together accounted for 2.02 million (14.15%) cases. 1.73 million cases were identified in sub- Saharan Africa. High morbidity and mortality rate from typhoid occurs in Sub-Saharan Africa, attributed to delay in diagnosis and unawareness of complications from the disease[3-5]. Despite improved health facilities, typhoid fever steeps up to be endemic in resource-limited countries[5]. Recently in Ethiopia, a 3 % pooled prevalence (about 2.4 million cases) of typhoid fever has been estimated over 10 (2010-2021) years[6].

Typhoid fever has a great impact on the socio-economic entities. Financial and time costs burden on households, and the need to improve health literacy. Patients with typhoid infection may spend weeks to several months at the hospital, keeping away from work areas. This brings about considerable difficulty in earning a living. With the advent of drug-resistant *S typhi*, commonly used antibiotics are less effective, and risks increase for complications and hospitalizations[7].

Typhoid fever affects almost all organs. Once in the body, *S. typhi* lodges in the bone marrow, an important blood-forming organ. Hematological abnormalities are commonly reported complications in typhoid fever[8,9]. The common hematological complications reported in typhoid fever patients are neutropenia, anemia leukopenia, and

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thrombocytopenia, but there are also possibilities of neutrophilia and moderate forms of leukocytosis. In light of scholarly papers, bone marrow suppression, histiocytosis, and hemophagocytosis are possibly contributing events disturbing peripheral blood cell counts[10].

The occurrence of infection in Ethiopia is frequent (as related to sanitation) which makes it a concern for the government[11]. Although treating typhoid fever with antibiotics can often revert abnormalities associated with the disease, some serious hematological complications may occur[12]. Even, nowadays, multidrug-resistant *Salmonella typhi* is prevalent, especially in low and middle-income countries[13]. In that regard, typhoid-associated complications such as hematological disturbances may worsen the mortality and morbidity from typhoid fever. Moreover, to date, up to the development of this study, no published data is available regarding hematological complications of typhoid fever in Ethiopia.

Therefore this study aims to asses hematological profiles of adult patients with Typhoid fever. Moreover this study would provide information to healthcare professionals about the hematological entities in typhoid fever, so that typhoid fever patients could receive appropriate care for possible hematological disturbances during the course of treatments.

## METHODS & MATERIALS

A Hospital-based comparative cross-sectional study was conducted between September and November 2023 at Dilla University General Hospital, Dilla, Ethiopia. The town is located in the South regional state of Ethiopia. The town is found at 365km from Addis Ababa, the capital city of Ethiopia. Dilla University General Hospital serves patients living in the Gedeo Zone and patients coming from the neighboring Sidama and Oromia regions [14]. The hospital has Inpatient, Emergency, NIKU, Main, TB, and microbiology laboratories. The hematology laboratory is included in the main laboratory. The study involves adult patients coming to Dilla University General Hospital presented with signs and symptoms of typhoid fever (cases), and
apparentely healthy adult controls who accompanied patients and those who came to the hospital for medical checkup during the study period.

### Eligibility Criteria

All clinically suspected, typhoid-confirmed cases and apparently-healthy typhoid-negative individuals (controls) fulfilling the inclusion criteria were included in this study. Patients who had started antibiotics before this study, pregnant or active breastfeeding women, individuals who had surgery and/or organ transplantation within one year, those with histories of liver diseases, renal diseases, hematological disorders, malaria, intestinal infections, hepatitis B Virus (HBV), hepatitis C Virus (HCV), and immune suppressants (drugs/HIV) states were excluded.

### Description of Study Variables

In this study selected hematological Profiles are dependent variables, while Socio demographic data: age, sex, residence, and marital status are independent variables.

### Sample Size Formulae

The sample size was calculated using a double population mean difference by assuming the two populations' mean difference of percent neutrophil count was 5, while 14 and 9 were percent values for σ1 & α2, respectively [15]. The sample size was calculated for different hematological parameters. We took the largest sample size among the parameters.

$$n \geq (Z\,1 - + Z\,1 - \beta)^2 * (\sigma 1^2 + \sigma 2^2)/E^2$$
$$n \geq (1.96 + 0.84)^2 * (14^2 + 9^2)/(65.0 - 60)^2$$
$$n \geq (7.84 * 277)/25$$
$$n \geq 87$$

Where,
n= number of samples for each group)
$Z1-\alpha/2$ = 1.96 (For a 5% significance level)
$Z1-\beta$ = 0.84 (For 80% power)
M1 =65.0% (percent mean of neutrophil count in cases)
M2 =60 (percent mean of neutrophil count in controls)
σ1 = 14 (Standard deviation of the cases)
σ2 =9 (Standard deviation of controls)
Thus, a minimum sample size of 87 is compulsory for each group**.**

### Data Collection Procedures

#### Questionnaire

A structured pre-tested questionnaire was used to collect socio-demographic and clinical data of the participants. Detailed medical history and records were examined thoroughly by nurses and physicians in the hospital. The questionnaire was written in English, and translated to Amharic.

### Clinical Data Collection Procedures

Multiple data collection techniques and sources were used to obtain clinical data. Before medical record reviewing and screening tests, careful observation of participants for symptoms of any diseases was made. Thorough evaluations of patients' medical history, medical record reviews, and screening tests were used to assess clinical data. The clinicians extensively reviewed the participant's medical records along with history takings for the history of liver diseases, renal diseases, hematological disorders, immune suppressants (drugs/HIV) states, and recent treatment with antibiotics. Parasitic infections, HBV, HCV, pregnancy, and HIV status were assessed through screening after getting permission from the participants unless known medical records and history were obtained. Histories of active breastfeeding states, recent blood donation, transfusion, and organ transplantations were assessed through medical record reviewing and/or history taking from the participants.

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**Laboratory Data**

Rapid stool antigen test and stool microscopy were used to detect *S. typhi* and parasitic infections respectively. One to two grams of formed stool or about 50 microns for lose tool were used for stool tests. Five milliliters of blood was collected into a serum separator tube for a Widal test and about 4ml into an Ethylenediamine tetra acetic acid (EDTA) tube for complete blood count (CBC). CBC was made using the ADVIA 560 Hematology analyzer (Siemens Healthcare Diagnostic family). In addition to rapid stool antigen test, a Widal test was performed on the control group to exclude adults with chronic carriage of typhoid fever.

**Data Quality Assurance**

To ensure the quality of the data, training was given to data collectors, and data was collected using a pretested questionnaire. Standard operating procedures were strictly followed during specimen collection and laboratory analysis procedure as per the WHO recommendations. Commercially available low, normal, and high-quality control reagents were used to check the reliability (accuracy and precision) of the data generated by the hematology analyzer.

**Data Analysis and Interpretation**

Data were entered and analyzed by Statistical Package for Social Sciences (SPSS) software (version 27, USA). The Kolmogorov-Smirnov and Shapiro- Wilk tests of normality were used. Descriptive statistics were used to determine the mean, median, standard deviation, and interquartile ranges of the variables. An Independent t-test for normally distributed data, and the Man-Whitney U test for non-normal data sets were used for comparisons of mean and median of each parameter between study groups respectively. The potential predictor variables with P-value < 0.05 were considered statistically significant.

**RESULT**

**Socio-Demographic Characteristics of the Study Participants**

A total of 174 participants aged between 18-62 years from outpatient and inpatient departments were involved in this study. Of the participants, 96 (55%) were males, and among typhoid- positive participants, the majority, 74% were from outpatient departments, and about 41(47%) were in the age group of 29-41 years. More than half of the participants (68%) were urban occupants and about one-fourth (24%) were non-governmental workers (Table I).

**Table – I: Socio-Demographic Characteristics of typhoid positive and negative groups (*n*=174)**

| Variables | | Number of participants (*n*=174) |
|---|---|---|
| | | Frequency (%) |
| Gender | Male | 96(55) |
| | Female | 78(45) |
| Age group | 18-28 | 16(9) |
| | 29-41 | 84(48) |
| | 42-52 | 52(30) |
| | 53-65 | 22(13) |
| Residence | Urban | 119(68) |
| | Rural | 55(32) |
| Marital Status | Married | 105(60) |
| | Unmarried | 56(32) |
| | Divorced | 13(8) |
| Education | Illiterate | 18(10) |
| | Read and write | 23(13) |
| | Elementary | 36(21) |
| | preparatory | 51(30) |
| | Higher | 46(26) |
| Occupation | Gov't Employee | 29(17) |
| | NGO | 46(26) |
| | Merchant | 32(17) |
| | Housewife | 33(18) |
| | Student | 25(14) |
| | Farmer | 14(8) |

**Comparisons of hematological parameters between typhoid positive and negative groups**

The hematological parameters between case and control groups were compared by the mean and median for normally and non-normally distributed parameters using Independent t-test and man Whitney U-test respectively. Statistically significant (P<0.05) decrease in WBC, neutrophil, RBC, Hgb, HCT, and platelet count were observed in the cases compared to the control group (Table II).

**Table – II: Comparison of hematological parameters between typhoid positive and negative groups (*n*=174)**

| Parameters | Cases(N=87) | Controls(N=87) | *p*-value |
|---|---|---|---|
| | Mean± SD | Mean± SD | |
| WBC×$10^3$/µl | 6.85±2.57 | 7.78±2.46 | 0.016 |
| Lymphocyte×$10^3$/µl | 2.34±0.80 | 2.45±0.82 | 0.371 |
| Eosinophil×$10^3$/µl | 0.50±0.29 | 0.48±0.26 | 0.649 |
| RBC×$10^6$/µl | 3.94±1.09 | 4.97±0.96 | <0.001 |
| Hgb(g/dl) | 11.31±3.36 | 14.36±2.35 | <0.001 |
| HCT(%) | 35.71±8.91 | 43.86±7.38 | <0.001 |
| Platelet×$10^3$/µl | 263.31±90.98 | 319.16±113.68 | <0.001 |
| | Median± IQR | Median± IQR | |
| Neutrophil×$10^3$/µl | 3.50±3.28 | 4.00±2.69 | 0.007 |
| Mnocyte×$10^3$/µl | 0.49±0.32 | 0.51±0.40 | 0.338 |
| Basophil×$10^3$/µl | 0.00±0.00 | 0.00±0.00 | 0.201 |

*SD= standard deviation, IQR= interquartile range, WBC= white blood cell , RBC= red blood cell, Hgb= hemoglobin, HCT= hematocrit.*

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**Comparisons of hematological parameters among typhoid positive and negative male groups**

As indicated in the table below, RBC, Hgb, HCT, and platelet were found to be low in typhoid-positive males. WBC, neutrophil, lymphocyte, and monocyte, counts were lower in typhoid-positive males than males without typhoid fever, but these differences were not statistically significant (Table III).

**Table – III: Comparison of hematological parameters between typhoid positive and negative male groups (*n*=96)**

| Parameters | Positive male(N= 48) | Negative male(N= 48) | *p*- value |
|---|---|---|---|
| | Mean± SD | Mean± SD | |
| WBC×$10^3$/ µl | 7.19±2.67 | 8.18±2.43 | 0.062 |
| Neutrophil×$10^3$/µl | 3.80±2.27 | 4.56±1.95 | 0.04 |
| Lymphocyte×$10^3$/µl | 2.26±0.79 | 2.38±0.88 | 0.472 |
| Eosinophil×$10^3$/µl | 0.59±0.28 | 0.56±0.25 | 0.611 |
| RBC×$10^6$/µl | 4.18±1.09 | 5.44±0.91 | <0.001 |
| Hgb(g/dl) | 12.04±3.27 | 15.30±2.10 | <0.001 |
| HCT(%) | 37.38±8.88 | 47.97±6.20 | <0.001 |
| Platelet×$10^3$/µl | 276.14±89.64 | 331.73±111.73 | 0.008 |
| | Median± IQR | Median± IQR | |
| Monocyte×$10^3$/µl | 0.56±0.32 | 0.67±0.42 | 0.214 |
| Basophil×$10^3$/µl | 0.00±0.00 | 0.00±0.00 | 0.184 |

**Comparisons of hematological parameters between typhoid positive and negative females**

Except for monocyte and basophil counts, all other parameters were normally distributed across female participants. The mean WBC, neutrophil, lymphocyte, RBC, and platelet counts were lower in typhoid-positive female subjects compared to apparently healthy typhoid-negative females. The median± IQR of monocyte and basophil were almost invariable among female subjects (Table IV).

**Table – IV: Comparison of hematological parameters between typhoid positive and negative female groups (*n*=78)**

| Parameters | Positive female (*n*=39) | Negative female (*n*=39) | *p*-value |
|---|---|---|---|
| | Mean± SD | Mean± SD | |
| WBC×$10^3$/µl | 6.43±2.40 | 7.29±2.44 | 0.123 |
| Neutrophil×$10^3$/µl | 3.07±1.91 | 4.01±1.96 | 0.036 |
| Lymphocyte×$10^3$/µl | 2.43±0.82± | 2.53±0.75s | 0.595 |
| Eosinophil×$10^3$/µl | 0.39±0.28 | 0.39±0.24 | 0.885 |
| RBC×$10^6$/µl | 3.66±1.04 | 4.40±0.65 | <0.001 |
| Hgb(g/l) | 10.43±3.29 | 13.21±2.15± | <0.001 |
| HCT (%) | 33.65±8.64 | 38.81±5.31 | 0.002 |
| Platelt×$10^3$/µl | 247.53±90.25 | 303.69±115.59 | 0.020 |
| | Median± IQR | Median± IQR | |
| Monocyte×$10^3$/µl | 0.37±0.23 | 0.36±0.24 | 0.780 |
| Basophil×$10^3$/µl | 0.00±0.00 | 0.00±0.00 | 0.705 |

**DISCUSSION**

Typhoid fever is associated with various hematological changes. Typhoid-associated hematological changes may involve either single or multiple hematologic profile alterations at a time[1,2]. Leukopenia remains the most common hematologic change observed in typhoid fever. In some occasions, leukocytosis may occur in typhoid infections[3]. Eosinophilia and thrombocytopenia are common, but not well-recognized hematological alterations in typhoid fever patients[4]. An inflammatory reaction following infection with typhoid fever results in some changes to hematological profiles[5]. A rare but serious typhoid-associated haemolytic anemia is also demonstrable in typhoid fever[6].

In this study, the mean WBC, RBC counts, Hgb, HCT, and Platelet counts were significantly low ($p< 0.05$) in typhoid-positive adults compared to apparently healthy control groups. Likewise, the median of absolute neutrophil count was lower in case groups. Regarding male participants, except the mean WBC count which was insignificantly low, all other parameters mentioned above were significantly low among male participants with typhoid fever. The mean absolute neutrophil count, RBC count, Hgb level, HCT, and platelet counts were lower among positive females compared to females with typhoid fever.

This study showed that the mean± SD of WBC count, 6.85 ± 2.5, and median of absolute neutrophil, 3.50±3.28 were significantly lower in the case groups compared to that of typhoid-negative adults, 7.78 ± 2.46 and 4.00±2.69 for WBC and neutrophil. This was consistent with a result reported by Etouke *et al* [7] and Dangana *et al.* [8]. Another study reported a similar mean WBC, and absolute neutrophil count between the cases and controls[9]. Another study reported a decrease in

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the mean absolute neutrophil count as did our study, but insignificantly high mean WBC count in the case group than in controls, contradicting the present study. The pathophysiology of neutrophil reduction in typhoid fever is multiplex, which includes endotoxins, cytokines including tumor necrosis factor, interleukin 6, and interferon γ promoting hemophagocytosis[10]. The works of Farmakiotis *et al*.[11] and Abro *et al*[12] support the current study in terms of the mean total WBC count between the groups ($p<0.05$). Low white blood cell count can be brought about by the modified adhesiveness of WBC to the endothelial layer of the blood vessels[13]. Metabolic activity in Salmonella typhi which unleashes toxins on the bone marrow can cause a failure to make enough blood components, such as white blood cells[14]. Sarkinfada *et al*.[15] found a significantly high mean percent neutrophil, but an insignificant increment in the mean total WBC count in cases compared to controls.

In this study the mean ± SD of RBC count was 3.94±1.09; Hgb, 11.31±3.36; HCT, 35.71 ±8.91 and were significantly lower than the mean ±SD of RBC count,4.97 ±0.96; Hgb, 14.36 ±2.35; HCT, 43.86 ±7.38 of controls ($p<0.05$). Similar results to the present study were reported by Emenuga *et al*[16] and all were statistically significant ($p<0.05$). Another study found a concordance of mean Hgb, and HCT values, but significantly higher mean RBC count between the cases and controls in order[7]. Qamar *et al*[17] found lower values of mean± SD of Hgb and HCT among typhoid-positive participants which were in line with the present study. The average Hgb and HCT levels were also found to be significantly lower in participants with typhoid in comparison to the values in healthy groups[8], supportive of our study. Certain hematological profiles, such as RBC and PCV among others have been affected by typhoid fever as it disrupts many parts of the body systems involving the bone marrow[18].

The present study revealed that the mean± SD of Platelet (263.31±90.98) in positive cases was low compared to that of typhoid-negative controls ($p<0.001$). The low mean± SD of platelet count in our study was in line with *Abro et al.* [12] and Darton *et al*. [19]. Another study revealed a significantly low platelet count among the cases compared to controls[7]. The mean platelet count of the present study agrees with studies by Qamar *et al*.[1] and Emenuga *et al.* [18] provided that significantly low mean platelet counts were found among typhoid positive group compared to controls in these studies. The high favorability of DIC during typhoid infection promotes platelet consumption, which results in low peripheral platelet counts[20].

The mean WBC, 7.19± 2.67; absolute neutrophil count, 3.80±2.27); platelet count, 276.14± 89.64; HCT, 37.38± 8.88; Hgb, 12.04± 3.27 and RBC count, 12.04± 3.2 of typhoid positive male cases were lower than typhoid negative male participants with mean WBC count, 8.18± 2.43; 4.56±1.95; platelet count, 331.73± 11.73; HCT, 47.97± 6.20; Hgb, 15.30± 2.10 and RBC count, 5.44± 0.91 in this study. The findings are in concurrence with studies by Ozougwu *et al.* [21],[22] (except for mean platelet count), and [23] except for statistical significance in mean WBC count for the latter two studies ($p<0.05$). Insignificantly higher mean platelet count was found among males with the disease than that of healthy male controls [22]. The introduction of *Salmonella Typhi* into the circulation brings about an inflammation that alters various hematological manifestations[7].

In this study, Hematological profile alterations accompanying in female patients with typhoid fever revealed a significant decrease in PCV, HB, RBC and platelet, whereas low but insignificant total WBC count in typhoid-positive females compared to their counterparts which were comparable to the works of Ndako *et al* [7] and Ozougwu *et al* [23]. This is also consistent with the work of Ifeany *et al*.[24], Dangana *et al.* [25], Okafor *et al.* [26], and Darton *et al*. [19]. The occurrence of low peripheral blood cell counts can be caused by the colonization of blood-making organs such as lymph nodes, spleen, tonsils, and bone marrow by *Salmonella typhi* markedly slowing down blood cell production[27].

## CONCLUSION

In this study, statistically significant differences in WBC, RBC, Hgb, HCT, and platelet were observed between typhoid fever patients as compared to apparently healthy typhoid negative participants. From the differential counts, the mean absolute neutrophil count showed a significant decrease among typhoid cases compared to controls.

## RECOMMENDATION

Based on the findings of this study, it is suggested that a complete blood count, among others, is required at the presentation of the disease not only for diagnostic purposes but also for early detection of the possible hematological changes associated with typhoid fever. Due to the limited area coverage of this study, a country-level study with a large sample size would be paramount to further understanding of hematological profiles associated with typhoid fever.

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**Authors Contribution**

**Amanuel Baye**: Writing – original draft, Writing – review & editing, Investigation, Resource, Conceptualization, Methodology, formal analysis, supervision, Process administration. **Moges Wordofa**: Writing–review& editing Conceptualization, Methodology, Formal analysis, Supervision, process administration. **Andualem Bayih:** Methodology, Formal anlysis, Investigation, Writing – review & editing**. Mitku Tessafa:** Methodology, Formal anlysis, Investigation**,** Writing– review & editing**. Jemal Alemu**: Writing – review & editing**,** Conceptualization, Methodology, Formal analysis, Supervision, Process administration.

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**Conflict of interest**
None

**Ethical approval**
The study was ethically approved by Departmental Research and Ethics Review Committee (DRERC) with reference number MLS/079/23.

**Additional information**
Additional information is considerable upon a reasonable request.

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