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Original Article

Changes In Hematological Parameters Of Typhoid Fever Patients At Pku Bantul Hospital, Yogyakarta

[1]Ninda Devita, [2]Muhammad Syafiq Riski, [3]Rian Marufi

[1] Department of Microbiology, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia
[2] Department of Otolaryngology, General Hospital of Wonosari, Yogyakarta, Indonesia
[3] Resident at the Department of Internal Medicine, Faculty of Medicine, Public Health and Nurse, Universitas Gadjah Mada, Yogyakarta, Indonesia

E-mail Corresponding: ninda.devita@uii.ac.id

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ABSTRACT

Background: *:* Typhoid fever causes changes in the results of hematological examination. Many factors influence hematological changes in thyphoid fever these changes. This study aims to determine the relationship between several patient characteristics and hematological changes in typhoid fever patients at PKU General Hospital, Bantul, Yogyakarta

Method: This is a cross-sectional study. A total of 85 patients diagnosed with typhoid fever at PKU General Hospital were included in this study. Hematological examination results and subject characteristics (sex, age, duration of fever) were taken from medical records. The relationship between subject characteristics and hematological changes was analyzed by Chi-Square test using Medcalc software.

Result: Anemia and leukopenia were found to be higher in female subjects (34.88% vs 17.14%; p=0.03 and 20.45% vs 9.75%; p=0.04). Age ≥45 years are associated with the incidence of anemia (18.61 vs 40.00; p=0.03). Leukopenia and thrombocytosis was higher in patients with a duration of fever < 1 week (p=0.02 and p=0.000).

Conclusion: Hematological changes in thyphoid fever are influenced by gender, age, and duration of fever before admission to the hospital.

INTRODUCTION

Typhoid fever is still an important problem in the world. WHO recorded the incidence of typhoid fever as many as 14.3 million worldwide in 2017. The Southeast Asian Region accounts for 14.1% of cases globally [1]. Indonesia is one of the developing countries in Asia with a high incidence of typhoid fever (> 100 cases per 100,000 population per year). Typhoid fever is the third most common disease in hospitalized patients in Indonesia with a total of 55,098 cases [2].

Typhoid fever has symptoms varying from mild symptoms (fever, headache, fatigue,

loss of appetite, diarrhea, or constipation) to severe symptoms (gastrointestinal bleeding, intestinal perforation, and encephalitis) [3]. These symptoms are not typical and are similar to other diseases such as dengue fever and malaria [4]. The definitive diagnosis of typhoid fever is culture using samples of the patient's blood, urine, stool, or bone marrow aspiration. This specific laboratory examination is rarely performed due to limited facilities and cost issues. The serological examination is an alternative such as the Widal test or IgM test. However, this examination has poor sensitivity or specificity [5,6].

Initial laboratory tests that can be done in limited conditions are routine blood tests. Typhoid fever causes hematological changes that can help diagnose and evaluate prognosis [7]. The study shows that low leukocyte counts are related to fever [4,8]. Leucocytosis is associated with a poor prognosis [7]. Anaemia and decreased hematocrit can occur [7]. Thrombocytopenia may be a marker of coagulation disorders in patients with severe symptoms [4,7–9].

Many factors affect laboratory results, including duration of fever before therapy, use of antibiotics, patient age, gender, history of vaccination, and virulence of the bacteria [4] The study shows that men who are diagnosed with typhoid fever have a significantly reduced leukocytes count compared to healthy subjects. Meanwhile, typhoid fever in women causes a decrease in platelet count compared to healthy subjects [9]. Other studies have shown that anemia and thrombocytopenia are more common in males than females. Women more often suffer from leukopenia (Ozougwu et al., 2016). However, other studies discussing the relationship of other characteristics with hematological changes in typhoid fever have not been widely reported. Study related to this matter is also still limited in Indonesia. Based on the description above, this study aims to observe the relationship between several patient characteristics and hematological changes in typhoid fever patients at PKU General Hospital, Bantul, Yogyakarta.

METHOD

This study is an analytic observational study with a cross-sectional study design. Data collection was carried out in July 2016 at PKU Bantul General Hospital, Yogyakarta. All data were taken from medical records at the PKU Bantul General Hospital, Yogyakarta.

The population in this study were all hospitalized at PKU Bantul Public Hospital for the period January 1, 2014 – December 31, 2015. Patients over 18 years of age were included in this study. Patients with other co-morbidities and patients with incomplete laboratory data were excluded. The method of selecting subjects was carried out using the consecutive sampling method.

Typhoid fever patients were diagnosed by specialist doctors based on clinical manifestations and laboratory investigations with widal titers ≥1/160 and tubes≥4. Demographic characteristics consist of gender, age., and duration of fever before diagnosis. Gender is divided into male and female. While age was divided into two groups, namely <45 years and ≥45 years. Duration of fever was defined as <2 weeks and > 2 weeks of fever.

Laboratory parameters taken were hemoglobin, platelets, and leukocytes. The hemoglobin parameter is then divided into anemia and normal with a cut point of <12 g/dL for women and <13 g/dL for men [10]. Leukopenia is defined when the leukocyte count is below 4000 x103/ µL [11]. Leukocytosis was obtained from the results of a leukocyte count above 11,000 x103/µL [11]. Platelet count is divided into thrombocytosis and thrombocytopenia. Thrombocytopenia is defined as a platelet count <150,000 x103/ µL while thrombocytosis is when the platelet count is > 450,000 x103/ µL [12].

Variables with categorical data are presented in the form of proportions (%). Meanwhile, numerical data are presented in the form of mean ± SD or median (min-max) depending on the distribution of the data.

Differences in changes in laboratory parameters between groups on demographic characteristics were analyzed using the Chi-Square test. All analyses used MedCalc software.

RESULT

This study was conducted retrospectively using medical record data from 2014 to 2015. A total of 277 typhoid fever patients at PKU Bantul Hospital consisted of 117 cases in 2014 and 130 cases in 2015. Patients who met the inclusion criteria were 169 patients. A total of 49 patients were excluded because have other co-morbidities (urinary tract infection 26, dengue 18, pneumonia 1, bronchitis 2, varicella 1, meningoencephalitis 1). Patients who were excluded due to incomplete laboratory data were 5 patients so the patients who entered the research subjects were 85 patients. This study was carried out after obtaining an Ethical Clearance from the Ethics Committee for Medical and Health Research, Faculty of Medicine, Universitas Islam Indonesia, and a Study Permit from PKU Hospital, Bantul.

Of the 85 subjects, 48.23% were male (**Table 1**). The mean age of the subjects was 37.08 ± 13.93 with 70.52% aged 18-44 years. The Tubex test is the main diagnostic tool for typhoid fever (67.06%). Most of the subjects came in the first week of fever (83.53%). Hematologic test results showed hemoglobin level, leukocytes, and platelets count within normal limits.

Table 1. Characteristic Subject

Respondent Characteristic Variables	Frequency (n)	Percentage (%)
Gender		
Male	41 (48,23)	48.23
Female	44 (51,76)	51.76
Age		
18-44	60 (70,52)	70.52
≥ 45	25 (29,41)	29.41
Fever duration before diagnosis		
<1 week	71(83,53)	83.53
>1 week	14(16,47)	16.47
Hemoglobin (g/dL) (mean±SD)	13,40 ± 1,83	
Leukocyte (x10^3/ µL) (mean±SD)	7,10 (2,80-20,80)	
Platelet (x10^3/ µL) (median (min-max))	189,00 (28,10-527,00)	

Changes in hemoglobin parameters in the form of anemia were found in 25% of the study subjects (**Table 2**). Leukopenia cases were found in 15.3% of subjects. While the increase in leukocytes or leukocytosis was found to be lower (10.6%). Thrombocytopenia was found in 17.6% of the study subjects. However, only 2.4% of subjects had thrombocytosis.

Table 1. Characteristic of Asthenopia, Accommodation Insufficiency and Screen Time

Characteristic	Frequency (n)	Percentage (%)
Anemia	21	25
Leukopenia	13	15.3
Leukocytosis	9	10.6
Thrombocytopenia	15	17.6
Thrombocytosis	2	2.4

Parameter changes on the hematologic examination were analyzed based on several characteristics of the study subjects. Anemia was found to be higher in female subjects (34.88% vs 17.14%; p=0.03). The decrease in leukocyte count (leukopenia) was also found to be higher in females (20.45% vs 9.75%; p=0.04). Sex does not affect changes in other parameters (**Figure 1**).

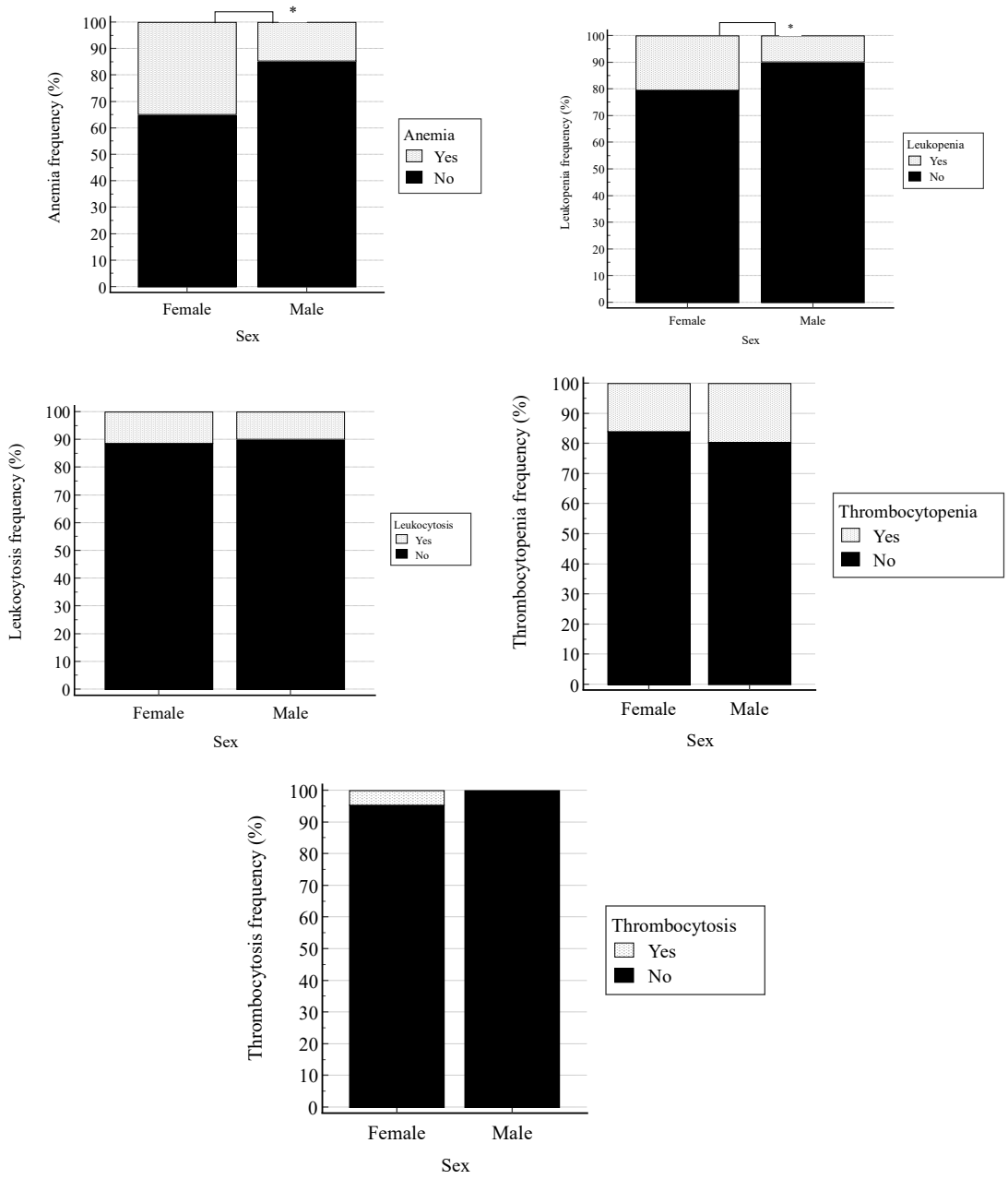

Figure 1. Changes of Hematological Parameter in Different Sex (* p significant < 0,05 with Chi-Square test)

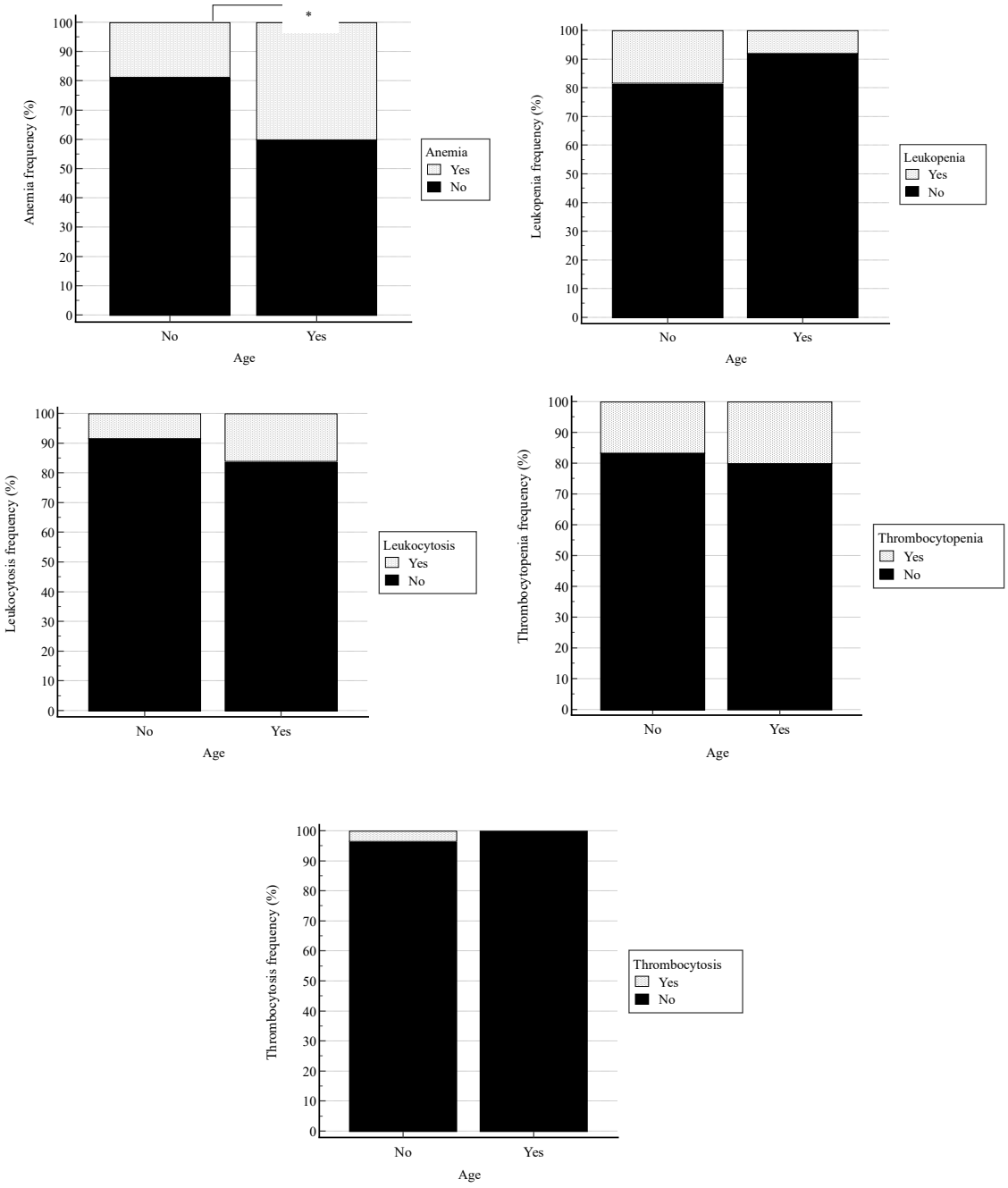

Figure 2. Changes of Hematological Parameter in Different Age Groups (* p significant < 0,05 with Chi-Square test)

We also analyzed the association between the duration of fever and hematological changes. Leukopenia was higher in patients with a duration of fever < 1 week (18,1% vs 0%; p=0,02). However, thrombocytosis is more common in patients hospitalized > 1 week of fever (0% vs 15,4%; p=0,000). Another parameter is not affected by the duration of the fever (Figure 3).

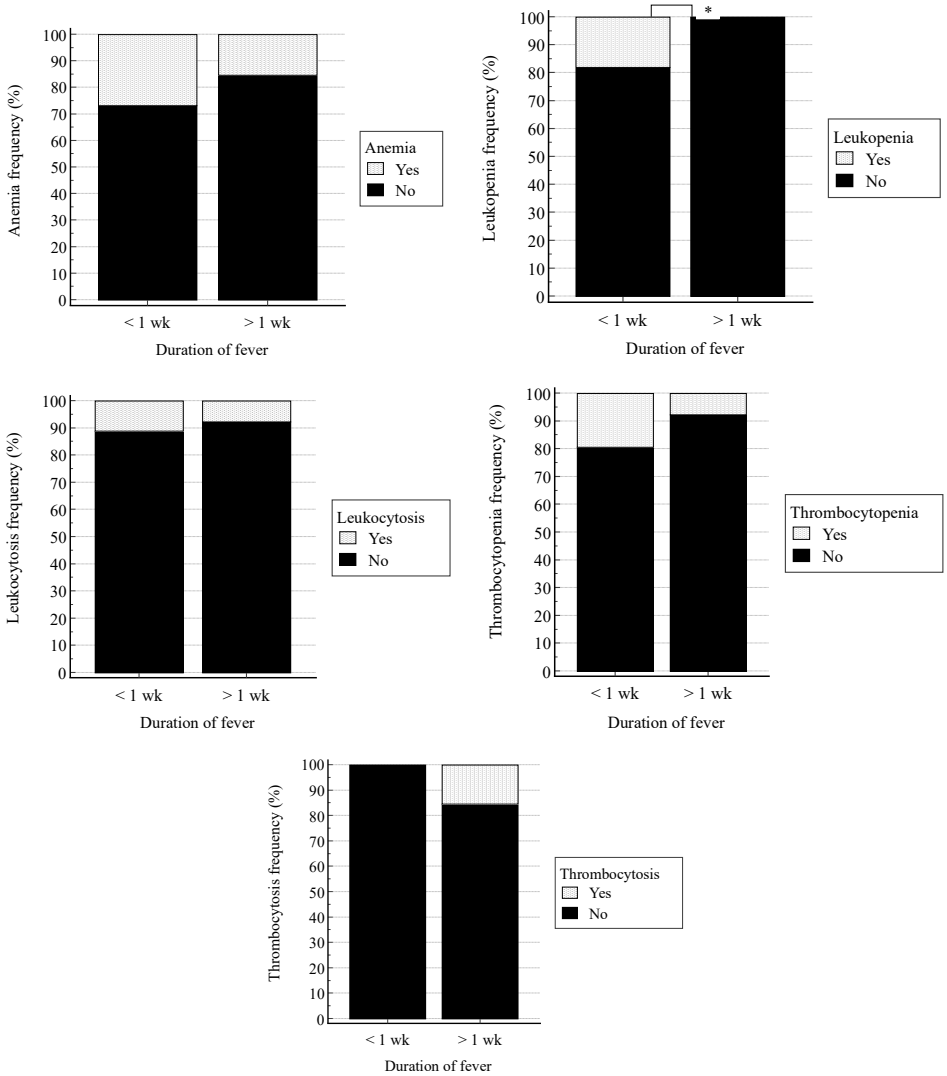

Figure 2. *Changes of Hematological Parameter in Different Age Groups (* p significant < 0,05 with Chi-Square test)*

DISCUSSION

This study involved 85 subjects with a distribution of 47.42% male and 52.58% female. The proportion of this study is almost the same as several previous studies where there were more female subjects than male subjects [13]. Meanwhile, other studies conducted found that the proportion of male subjects suffering from typhoid fever was higher than that of female subjects [8]. The differences that occur are likely due to differences in population. Research shows the incidence of typhoid fever is independent of gender. This condition occurs in all age groups [14,15].

The mean age of the subjects was 37.08 years (SD ±13.39 years). The most age group that suffers from typhoid fever is the age group 18-44 years (70.52%). Age 18-44 years is the age of school and work. This age group often does activities outside the home. Activities outside the home increase the risk of consuming food contaminated with *Salmonella typhi* [14,16]. Study shows that the relationship between washing hands before eating, eating habits, and where to eat is related to the incidence of typhoid fever in the productive age group [13].

Most patients come to the hospital within two weeks with a fever. Another study with typhoid fever patients in hospitals also obtained similar results [8,13]. This shows that the public is quite aware of infectious diseases such as typhoid fever.

Typhoid fever is a complex disease with several stages of disease t. In the incubation phase, the patient is asymptomatic but the bacteria infect macrophages and circulate throughout the reticuloendothelial system. During the symptomatic phase, bone marrow suppression and hemophagocytosis may occur. Evidence suggests that there is an arrest of myeloid maturase and a decrease in the number of erythroblasts and megakaryocytes in the bone marrow. This process can cause changes in hematologic parameters [7,9,17].

In this study, anemia was found in 25% of cases. Anemia is the main hematologic abnormality in typhoid fever patients. Other studies found anemia was present in more than half of the study subjects [17,18]. The hemoglobin of patients with typhoid fever is lower than normal controls [7]. The main cause of this disorder is due to bone marrow suppression and hemophagocytosis due to infection with *Salmonella typi* [7]. A study shows that most of the anemia in typhoid fever is iron deficiency anemia. Decreased serum iron due to inflammation by Salmonella infection will increase the degradation of ferroportin by hepcidin so that iron is difficult to absorb and accumulate in enterocyte cells [19]. Nutritional status and co-infection are suspected of contributing to anemia [17]. However, if severe anemia occurs, gastrointestinal bleeding may be suspected or a secondary infection such as malaria may occur [9].

When analyzing the relationship between several subject characteristics, the incidence of anemia was significantly higher in the female group than in the male group. Other studies have shown that decreased hemoglobin levels are more common in female typhoid fever patients than in male patients [20]. This decrease may be due to menstrual blood loss or problems with iron malnutrition in women [9]. Anemia is also more common at age ≥45 years. This is presumably because the immune system decreases with age. A decreased immune system causes infections to become more severe [16].

Thrombocytopenia is the second rank that is often found in this study. The results are the same as the study by Abro where 40% of typhoid fever patients had thrombocytopenia [18]. The main mechanism is decreased platelet production or increased destruction by the reticuloendothelial system or DIC. The presence of secondary infections such as dengue fever may play a role in this condition [8].

In this study, the incidence of thrombocytopenia did not differ between sexes and age groups. These results are the same as a study conducted in Ghana, thrombocytopenia was not affected by gender in various age groups [21]. Other studies have shown a greater reduction in platelet count in men than in women [9,20]. This difference may be due to the duration of the subject's fever at the hospital which is different from previous studies. In this study, most of them came in the first two weeks of fever. The first two weeks are the acute phase of the disease. The acute phase is characterized by initial septicemia leading to toxic bone marrow suppression. This causes thrombocytopenia. Thrombocytopenia can contribute to the severity of gastrointestinal bleeding in patients with typhoid fever [17].

The most common change in leukocyte count is leukopenia followed by leukocytosis. Other studies have shown similar results [8,18]. The decreased number of leukocytes in typhoid fever is due to depression of the bone marrow. Leukopenia is in line with the severity of disease symptoms and is temporary [22]. This is evidenced by the results of this study that leukopenia is associated with the duration of fever before admission to the hospital. The proportion of leukopenia was found more in patients with fever <2 weeks duration ($p<0.05$).

Analysis of the relationship between leukopenia and gender showed that leukopenia was related to female gender. Several other studies have shown different results. The leukocyte count is not related to gender [21,23]. This difference is probably due to differences in the age groups studied. The

results of another study with almost the same subject found a relationship between sex and leukocyte count. Typhoid fever in males causes anemia and thrombocytopenia but not leukopenia. This condition may be due to bone marrow depression and more severe hematopoiesis in women. The fact that men are more likely to be exposed to *Salmonella typi* leads to repeated exposure in men. Repeated exposure to bacteria causes local mucosal immunity in the form of a stronger IgA response [20].

Typhoid fever causes changes in the patient's hematological parameters. The most common changes are anemia, thrombocytopenia, and leukopenia. Typhoid fever should be suspected as the cause of fever with these hematological abnormalities. The hematological examination should be examined early in patients with fever to help determine the diagnosis of typhoid fever.

Patient characteristics such as sex, age, and duration of fever affect changes in hematological parameters. Anemia is more common in female patients or patients aged ≥ 45 years. Leukopenia is influenced by female sex and duration of fever < 1 week. This condition may affect the clinical patient. Clinicians should be more aware of patients with these characteristics.

CONCLUSION

Hematologic changes that are often found in patients with typhoid fever are anemia, thrombocytopenia, and leukopenia. These changes are influenced by gender, age, and duration of fever before admission to the hospital.

There are quite several subjects in this study so it is sufficient to describe the data in the population. However, this study is a cross-sectional study. Further research needs to be carried out using longitudinal to determine the pattern of hematological changes in typhoid fever patients. A study linking hematological changes with the patient's clinical condition is also needed to determine the interaction between them.

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