

**CHARACTERISTIC OF CHRONIC MYELOGENOUS LEUKEMIA PATIENTS AT THE POLYCLINIC OF ONCOLOGY, DR. SOETOMO GENERAL HOSPITAL, SURABAYA IN 2017**

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**ABSTRACT**

**Background:** Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm because of the reciprocal translocation of chromosome 22 to chromosome 9. In the United States, the incidence of CML is 1.9 cases per 100,000 people. Whereas in Indonesia, there is no specific national data on CML prevalence, especially regarding the clinical picture even though cancer cases reach 1.4 per 1,000 population. **Objective:** Evaluate the characteristics and clinical features of CML patients in Dr. Soetomo General Hospital, Surabaya. **Method:** This is a cross-sectional descriptive study with data on the medical records of CML patients in the 2017 period at the Dr. Soetomo General Hospital, Surabaya. The sample in this study was CML patients with positive Breakpoint Clusters Region-Abelson (BCR-ABL), having a minimum age of 18 years and equipped with epidemiological data, complete blood count data, and peripheral blood smear data. **Result:** Thirty-three patients met the study criteria. The sample was predominantly male, with a ratio of 1.06 : 1 to female patients with a median age of 40 years. Splenomegaly was found in 87.9% of patients. The average results of leukocyte, platelet, and hemoglobin counts were  $254.58 \times 10^3 / \mu\text{L}$ ,  $557 \times 10^3 / \mu\text{L}$ , and 9.55 g / dL. From the results of peripheral blood smear obtained normochromic normocytic anisopoikilocytosis erythrocyte (57.6%), all patients had an image of increased leukocytes with blast presence in 97% of patients, and 51.5% had the image of an increase in platelets and the discovery of giant platelets in 33.3% of patients. **Conclusion:** The sample is predominantly male with the highest incidence at a younger age range of 21-30 years; The clinical characteristics of high leukocytosis with various stage of maturation and a tendency to develop grade 2 normocytic normochromic anemia and thrombocytosis was found in the patients.

**Keywords:** Characteristics, Clinical Features, Chronic Myelogenous Leukemia

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## Background

Chronic myelogenous leukemia (CML) is a myeloproliferative cell malignancy caused by abnormal hematopoietic cells due to reciprocal translocation of chromosome 22 with chromosome 9, resulting in Philadelphia chromosomes that have BCR-ABL oncoproteins resulting in abnormal blood cell formation and triggering CML. CML can occur at any stage of life, although it is less common in children (Goldman, 2003).

In the United States, in 2019, cancer is one of the leading cause of death after heart disease. It is estimated that around 1.7 million people are diagnosed with cancer, and of these number estimated new cases and deaths from CML are 0.5% (8,990) and 0.2% (1,140) with a 5-year life expectancy of 69.2%. CML incidence is 1.9 cases of 100,000 people (Howlander *et al.*, 2019). In Indonesia alone, the prevalence of cancer cases reaches 1.4 of 1,000 population, but there is no specific national data on CML especially about the clinical profile (Kemenkes RI, 2013).

Until now, the etiology of CML is unknown. The only risk factor that is known to influence the incidence of CML is exposure to ionizing radiation (Atul & Hoffbrand, 2014). This was discussed earlier in studies conducted on Japanese atomic bomb victims and in patients who received radiotherapy for ankylosing spondylitis (Goldman, 2003). Besides, CML is thought to have no association with family relationships because no increased risk of CML was found in monozygotic twins or relatives of patients. Although radiation exposure is a risk factor for CML, it is still unknown why and how certain groups of people can suffer from CML (O'Brien, Vose dan Kantarjian, 2011).

CML is divided into 3 phases, namely the chronic phase, the acceleration phase, and the blast crisis phase. A small number of patients in the chronic phase will develop into a phase of acceleration and blast crisis phase. This can occur due to additional genetic changes in leukemia stem cells that can be detected by cytogenetic analysis (Shah & Arceci, 2014). Some patients diagnosed with CML have no symptoms and are often found during routine check-ups. In the chronic phase CML, symptoms that appear are usually caused by anemia and splenomegaly that occur, such as fatigue, weight loss, malaise, and feeling full or pain in the left upper quadrant of the

abdomen. Splenomegaly is found in 40% - 50% of cases. Accelerated phase CML is usually characterized by worsening anemia, splenomegaly, and sometime other organ infiltration, whereas the CML blast crisis phase has the same picture as acute leukemia (Jabbour & Kantarjian, 2018). Laboratory features seen in peripheral blood of CML patients may consist of anemia, thrombocytosis, leukocytosis with a shift to the left, decreased neutrophil alkaline phosphatase (NAP), hyperuricemia, and elevated serum B12 levels. While on bone marrow examination, hypercellularity and bone marrow stroma fibrosis will be found in several cases (Raharjo, 2018).

The existence of this study is to evaluate the characteristics and clinical features of CML patients in Dr. Soetomo General Hospital, Surabaya. The existence of this study is expected to help add insight into the characteristics and clinical features of CML patients.

## Objective

In general, this study aims to evaluate the clinical profile of CML patients in RSUD. Dr. Soetomo, however, the specific objectives of this research include evaluating the characteristics of CML patients consisting of age, sex, and enlargement of the spleen, the results of a complete blood count of CML patients consisting of hemoglobin, leukocyte, and platelet counts, and the results of peripheral blood smears in CML patients who include the appearance of erythrocytes, leukocytes, and platelets.

## Method

This research is a cross-sectional descriptive study by reviewing secondary data in the form of medical records of new CML patients in 2017 at the Oncology Polyclinic, Dr. Soetomo General Hospital, Surabaya. This study has received ethical approval from Dr. Soetomo General Hospital committee of the health research ethics with certificate number No. 0786 / KEPK / XI / 2018. Samples in this study were CML patients with positive BCR-ABL that diagnosed using quantitative real-time PCR Cepheid Genexpert BCR-ABL, had the same age or more than 18 years, and were equipped with the data needed in the study. These data are epidemiological data that includes age and sex, physical examination

data, namely the presence of enlarged spleen, complete laboratory blood count data including hemoglobin, leukocytes, and platelets to evaluate the occurrence of anemia, leukocytosis, thrombocytopenia, and thrombocytosis as well as peripheral blood smear data. Include the impression of erythrocytes, the impression of leukocytes, the percentage of eosinophils, the percentage of basophils, the presence of blasts, and the impression of platelets. Patients are said to have anemia if the hemoglobin level is below 13.3 g / dL for men and below 11 g / dL for women and anemia that occurs will be graded based on criteria from the National Cancer Institute which is grade 1 for the lower limit of normal values up to 10 g / dL, grade 2 for 8-10 g / dL, grade 3 for 6.5-7.9 g / dL and grade 4 for <6.5 g / dL. Patients are said to have leukocytosis when the leukocyte count is more than  $10 \times 10^3 / \mu\text{L}$ . Patients are said to have

thrombocytosis if the platelet count is more than  $450 \times 10^3 / \mu\text{L}$  and thrombocytopenia if it is less than  $150 \times 10^3 / \mu\text{L}$ . The results of the study were collected and processed with Microsoft Excel 2010 application and Statistical Package for Social Sciences (SPSS) version 17.0 then presented in tabular form.

### Result

There were 33 patients diagnosed with CML with a positive BCR-ABL and fulfilled the established criteria. In table 1, it can be noted that the number of males is higher than females with a ratio of 1.06: 1. The age range in this study is 18-69 years, with the age group 21-30 years as the most frequent, and there are only 6% of patients over 60 years old. The mean age of patients was 40.63 years, with median of 40 years old. Magnification of the spleen or splenomegaly can be found in 87.9% of patients.

**Table 1. Characteristics of CML Patients.**

Variable	Results
<b>Gender</b>	
Male	17 (51.5%)
Female	16 (48.5%)
<b>Age</b>	
<=20	1 (3%)
21-30	10 (30.3%)
31-40	6 (18.2%)
41-50	7 (21.2%)
51-60	7 (21.2%)
>60	2 (6%)
Mean	40.63
Median	40
Range	18-69
<b>Splenomegaly</b>	<b>29 (87.9%)</b>

In the results of a complete blood count before treatment, the mean and median leukocytes were sequenced at  $254.58 \times 10^3 / \mu\text{L}$  and  $224.9 \times 10^3 / \mu\text{L}$  with a range of  $11.51-636 \times 10^3 / \mu\text{L}$ ; average and median platelets respectively of  $557 \times 10^3 / \mu\text{L}$  and  $494 \times 10^3 / \mu\text{L}$  with a range of  $122-1775 \times 10^3 / \mu\text{L}$ ; the mean and

median Hb was  $9.55 \text{ g / dL}$  and  $9.3 \text{ g / dL}$ , respectively, ranging from  $5.3$  to  $13.2 \text{ g / dL}$ . From these results, 30 patients had anemia, 18 thrombocytosis patients, two thrombocytopenia patients, and all patients had leukocytosis as listed in table 2.

**Table 2. Complete Blood Count Results**

Variable	Results
<b>Hb</b>	
Mean	9.55
Median	9.3
Range	5.3-13.2
<b>Leukocyte</b>	
Mean	254.58
Median	224.9
Range	11.51-636
<b>Platelet</b>	
Mean	557
Median	494
Range	122-1775
<b>Anemia</b>	
	30 (90.9%)
Grade 1	10 (30.3%)
Grade 2	15 (45.5%)
Grade 3	3 (9.1%)
Grade 4	2 (6%)
<b>Leukocytosis (&gt;10.000)</b>	
	33 (100%)
<b>Thrombocytosis (&gt;450.000)</b>	
	18 (54.5%)
<b>Thrombocytopenia (&lt;150.000)</b>	
	2 (6%)

The results of peripheral blood smear in this study were dominated by normochromic normocytic anisopoikilocytosis erythrocytes (57.6%), all patients had an impression of increased leukocytes with blast presence in

97% of patients, and more than half of patients (51.5%) had an impression of increased platelets and the discovery of giant platelets in 33.3% of patients which can be seen in table 3.

**Table 3. Peripheral Blood Smear Results**

Variabel	Hasil	Variabel	Hasil
<b>Leukocyte</b>		<b>Erithrocyte</b>	
Impression		Normochromic, Normocytic	4 (12.1%)
Increased	33 (100%)	Normochromic, Normocytic, Anisocytosis	6 (18.2%)
Normal	0	Normochromic, Normocytic, Anisopoikilocytosis	19 (57.6%)
%Eosinophil		Normochromic, Normocytic, Poikilocytosis	1 (3%)
Increased	7 (21.2%)	Hipochromic, Anisopoikilocytosis	3 (9.1%)
Median	3%		
Range	0.1% - 10%		
%Basophil		<b>Thrombocyte</b>	
Increased	28 (84.8%)	Impression	17
Median	4%	Increased	(51.5%)
Range	0.3% - 22%	Normal	15 (45.5%)
%Promyelocyte		Decreased	1 (3%)
Median	11%	Giant Platelet (+)	11 (33.3%)
Range	3% -24%		
%Myelocyte		<b>Blast</b>	
Median	12.5%	Presence	32 (97%)
Range	2% -32%		13 (39.4%)
%Metamyelocyte		<5%	4 (12.1%)
Median	7%	5-10%	15 (45.5%)
Range	2% -20%	>10%	

## Discussion

### Characteristics of CML Patient

In this study, sample is dominated by men with 17 patients (51.5%), with a ratio between men and women of 1.06: 1. These results were lower than epidemiological studies, which have been done before, where the ratio of men is 1.2 to 1.7. This difference can be caused by much larger sample size in the study (Höglund *et al.*, 2015). Even so, the results of this study are matched with almost all studies of the epidemiology of CML, which found that CML is more common in men than women in Western countries and other countries in asia (Au *et al.*, 2009). Men will be more at risk of developing CML because they have more

target cells. The target cell in question is the cell of origin in the case of radiation-induced CML or sporadic cases. This study reveals the idea that the essential cause of differences in the number of sexes is caused by differences in the number of target cells at risk for neoplastic transformation, higher risk per target cell, or both (Radivoyevitch *et al.*, 2014).

The mean age was 40.63 years with median of 40 years. There are only two patients (6%) who are in the age range above 60 years. This result is in line with the results of a study conducted at Hasan Sadikin Hospital, Bandung, with mean age and median, respectively 41.5 years and 42 years (Sumantri *et al.*, 2019). However, the two results are still

smaller than the results obtained in Western countries. In Western countries, the median range varies from 56 to 66 years (Höglund *et al.*, 2015). In another multicenter study also found a significantly higher average age of 57 years old, with 40% of the sample being in the age range above 60 years (Kantarjian *et al.*, 2002). These results are far different from the results of studies that have been conducted in Indonesia. This difference is likely due to genetic factors and differences in sample life expectancy. Even so, the results of the age group of CML patients in this study where most are in the age range of 21-30 are in line with the results of studies that have been conducted in Ethiopia (Fentie *et al.*, 2019).

The spleen is the largest lymphoid organ, making it susceptible to involvement with hematological malignancies such as leukemia. The involvement in question is the existence of extramedullary hematopoiesis in leukemia, which can affect the enlargement of the spleen and is known as infiltrating splenomegaly (Chapman & Azevedo, 2019). Splenomegaly was found in 87.9% of the sample. These results are not much different from research conducted at the Sanglah Hospital, Bali, where 96.6% of patients experienced splenomegaly (Kartawan *et al.*, 2016). However, both of these results are much higher than what Jabbour *et al.* got where the splenomegaly presence was 40-50% of all CML cases (Jabbour & Kantarjian, 2018). In a study conducted at Cipto Mangunkusumo Hospital, Jakarta, the presence of splenomegaly was also much lower at 33% of the sample, although there were samples that had received therapy in the study (Reksodiputro *et al.*, 2010). If evaluated through imaging, the spleen appearance is not specific and looks similar to lymphoma (Sjoberg *et al.*, 2018).

### Complete Blood Counts

In this study, all samples had high leukocyte counts with an average of  $254.58 \times 10^3 / \mu\text{L}$  and a median of  $224.9 \times 10^3 / \mu\text{L}$ . These results are in line with other studies with samples that have never been given therapy, one of which is research conducted in Algeria. In that study, a high leukocyte count was found with a median of  $346 \times 10^3 / \mu\text{L}$  (Entasoltan *et al.*, 2017). Much lower results were obtained in other studies with samples that had received therapy, such as interferon, hydroxyurea, or tyrosine kinase inhibitors

(Reksodiputro *et al.*, 2010). Whereas, the mean and median sequences were  $557 \times 10^3 / \mu\text{L}$  and  $494 \times 10^3 / \mu\text{L}$  for platelet counts. Similar results were obtained in a study conducted at the Sanglah Hospital, Bali, where the average platelet count is  $507.7 \times 10^3 / \mu\text{L}$  and  $392 \times 10^3 / \mu\text{L}$ . Whereas, the mean and median sequences were  $557 \times 10^3 / \mu\text{L}$  and  $494 \times 10^3 / \mu\text{L}$  for platelet counts. Similar results were obtained in a study conducted at the Sanglah Hospital, Bali, where the average platelet count is  $507.7 \times 10^3 / \mu\text{L}$  and  $392 \times 10^3 / \mu\text{L}$  (Kartawan *et al.*, 2016), which indicates that platelet count will tend to increase in CML cases. This statement was strengthened by the presence of 54.5% of patients who had thrombocytosis in this study and as many as 61% of patients in a study that had been conducted in several hospitals in Indonesia (Reksodiputro *et al.*, 2015). Besides, CML patients tended to be anemic, were in this study, the mean and median hemoglobin sequences were 9.55 g / dL and 9.3 g / dL, respectively, with 90.9% of patients experiencing anemia. Anemia that occurs most is in grade 2 (moderate), namely in 45.5% of the sample. This is matched with research conducted in Pakistan, where all patients have anemia, and grade 2 anemia is the most common in 46.9% of patients (Chang *et al.*, 2015).

### Peripheral Blood Smear

In this study, the impression of erythrocytes was dominantly normochromic normocytic with anisopoikilocytosis, the impression of leukocytes increased, and as much as 51.5% of patients had the impression of an increase in platelets and 33.3% of patients found giant platelets. The impression of erythrocytes and leukocytes in similar with studies that have been conducted at the Dr. Mohammad Hoesin Hospital, Palembang, where it was found that anemia that occurs in CML cases is mostly normochromic normocytic anemia and also supported by studies conducted in Pakistan. Even so, slightly different results were obtained on the impression of platelets, which was in research at the Dr. Mohammad Hoesin Hospital, Palembang, the impression of platelets tends to be regular with the presence of giant platelets in only 4.7% of samples (Rahadiyanto *et al.*, 2014; Chang *et al.*, 2015). However, this research is still in line with the results obtained in the research at Dr. M

Djamil Hospital, Padang, where the impression of platelets tends to increase in CML patients (Rendra *et al.*, 2013).

The study also found an increase in the percentage of basophils in 84.8% of patients with a median of 4% and an increase in the percentage of eosinophils in 21.2% of patients with a median of 3%. The different results are found in the studies that have been conducted at the Dr. M. Djamil Hospital, Padang, where patients with an increase in the percentage of eosinophils are more numerous than basophils. In that study, the increase in the percentage of eosinophils and basophils, respectively, was 31.25% and 6.25% of the sample (Rendra *et al.*, 2013). Even so, the median percentage of basophils is still in line with research conducted in Algeria, where the median percentage of basophils is 3.7% (Entasoltan *et al.*, 2017). Blast presence is almost always obtained (97%), where 39.4% of patients have a blast percentage below 5%, 12.1% have a percentage in the range of 5-10%, and 45.5% of patients have a percentage of more than 10%. Different results were obtained in the epidemiological study of CML conducted in several hospitals in Indonesia, where 64% of patients had a blast percentage below 5%, and only 12% of patients had a percentage of more than 10%. This indicates that the ratio of the chronic phase compared to other phases is smaller in this study than the study (Reksodiputro *et al.*, 2015).

### Conclusion

Based on the research objectives to be achieved and the results of research that have been carried out, the following are conclusions regarding the clinical profile of CML patients in Dr. Soetomo General Hospital, Surabaya in 2017, namely: CML is more common in men (1.06: 1) with a median age of 40 years and has the highest incidence at a younger age range than studies conducted in countries West that is 21-30 years. All CML patients who have not received therapy have high leukocytosis with an average of  $254.58 \times 10^3 / \mu\text{L}$  and have a tendency to develop grade 2 anemia (45.5%) with an average of 9.55 g / dL and thrombocytosis (54.5%) with an average of  $557 \times 10^3 / \mu\text{L}$ . Peripheral blood smear is dominated by normochromic normocytic erythrocytes with variations in shape and size (anisopoikilocytosis), increase in the number of leukocytes with various stages of

maturation, increase in the percentage of basophils in the majority of patients (84.8%), blast presence that is found in almost all patients (97 %) and a tendency for increased platelets in which 33.3% of patients had giant platelets.

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