CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3229224

Available online at: http://www.iajps.com Research Article

IDENTIFICATION & COMPARISON OF HAEMATOLOGICAL INDICES & CLINICAL CORRELATES OF FLT3 MUTATION IN AML AND ALL

Aamir Ramzan[1], Ikramdin Ujjan[2], Kiran Aamir[3], Irum[4], Muhammad Sarwar Khan[5], Sana[6], Sadia Shahmeer[7]

Dept. of Pathology - Liaquat University of Medical & Health Sciences, Jamshoro[1, 3, 5 & 7]
Dean - Basic Medical Sciences - Liaquat University of Medical & Health Sciences, Jamshoro[2]
Dept. of Pathology – Peoples University of Medical & Health Sciences, Shaheed Benazirabad[4]
Consultant Hematologist, Hyderabad[6]

Article Received: March 2019 **Accepted:** April 2019 **Published:** May 2019

Abstract:

BACKGROUND: *Acute leukemia is a worrying condition that merits early diagnosis & treatment to attain a positive prognosis. Molecular characterization helps in this regard and has thus been the focus of several studies recently but since molecular characterization is an intricate process, easily detectable hematological indices may serve as correlates of FLT3 mutation in the disease, serving the same purpose as molecular characterization but a lesser difficulty level and a lower cost.*

OBJECTIVE: *To determine and compare the hematological indices and clinical correlates of FLT3 mutation in acute myelogenous leukemia and acute lymphoblastic leukemia.*

METHODOLOGY: *This descriptive analysis was carried out from January 2018 to December 2018 upon a sample of 94 newly diagnosed cases of acute leukemia (chosen via non-probability, consecutive sampling) presenting to the Dept. of Pathology – Liaquat University of Medical & Health Sciences, Jamshoro. Data obtained from laboratory records and patient interviews was recorded into a self-structured questionnaire after taking written informed consent. The data obtained was analyzed using SPSS v. 20.0.*

RESULTS: *The mean age of the sample stood at 41 years (±19 SD). 59.57% of the sample comprised of males while the remaining 40.43% were females. Among the total of 94 patients studied, polymerase chain reaction demonstrated FLT3 mutations in 6 (11.32%) of 53 AML patients and 2 (4.88%) of 41 ALL patients. Among the hematological and clinical findings most closely correlated with FLT3 mutation, WBC was the most statistically significant.*

CONCLUSION: *After careful consideration, it can be concluded that no significant hematological correlates were identified, other than WBC count.*

KEYWORDS: *Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Clinical Correlates, Hematological Indices & White Blood Cell Count.*

Corresponding author:

Dr. Aamir Ramzan,
MPhil Scholar - Department of Pathology,
Liaquat University of Medical & Health Sciences, Jamshoro
***Email Address**: aamir_ramzan2002@yahoo.com*
***Contact**: +92-333-7007552*

QR code

Please cite this article in press Aamir Ramzan et al., ***Identification & Comparison Of Haematological Indices & Clinical Correlates Of Flt3 Mutation In AML And ALL.,*** *Indo Am. J. P. Sci, 2019; 06(05).*

INTRODUCTION:

Research has shown an increase in the global incidence of leukemia in recent years. In 2016, there were 467,000 new cases of leukemia and 310,000 leukemia deaths. Leukemia was responsible for 10.2 million disease adjusted life years. Leukemia developed in 1 in 118 men and 1 in 194 women worldwide. Between 2006 and 2016, the global leukemia incidence increased by 26% from 370,482 to 466,802 cases. **[1]**

Leukemia refers to malignancies of white blood cells. The malignancies are rare and arise from hematopoietic precursors. **[2]** This disease is divided and sub-divided into many types. Acute leukemia, as the name suggests, comprises of malignant aberrations that are quickly fatal if not treated. **[3]** Their characteristic feature is sudden uncontrolled growth of immature hematopoietic cells at the cost of normal marrow function. The two most common forms, relevant to this study are Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML). **[4]**

ALL, a malignant disease, arises from an array of numerous aberrations at the genetic level in a solitary lymphoid progenitor (B or T), altering the normal proliferation of blast cells, increasing survival, changing the matured form, and consequently resulting in the fatal buildup of leukemic cells. **[5]** The aberration events can further be sub-classified on the basis of the different stages of T or B-cell maturation, the knowledge of these individual sub-stages is therapeutically not useful, and serves no purpose other than of recognition of B-cell, B-cell precursor, T-cell, and early T-cell precursor stage. **[6]**

AML, the most frequent acute leukemia in adults, **[7]** is genetically typified by the accretion of somatically acquired genetic changes in hematopoietic progenitor cells altering normal mechanisms of proliferation and differentiation. Thus resulting in accumulation of myeloid lineage blasts cells in the bone marrow. The cells disturb routine process of hematopoiesis, and lead to failure of the bone marrow. The said failure is the commonest reason leading to eventual death among patients of AML. **[8]**

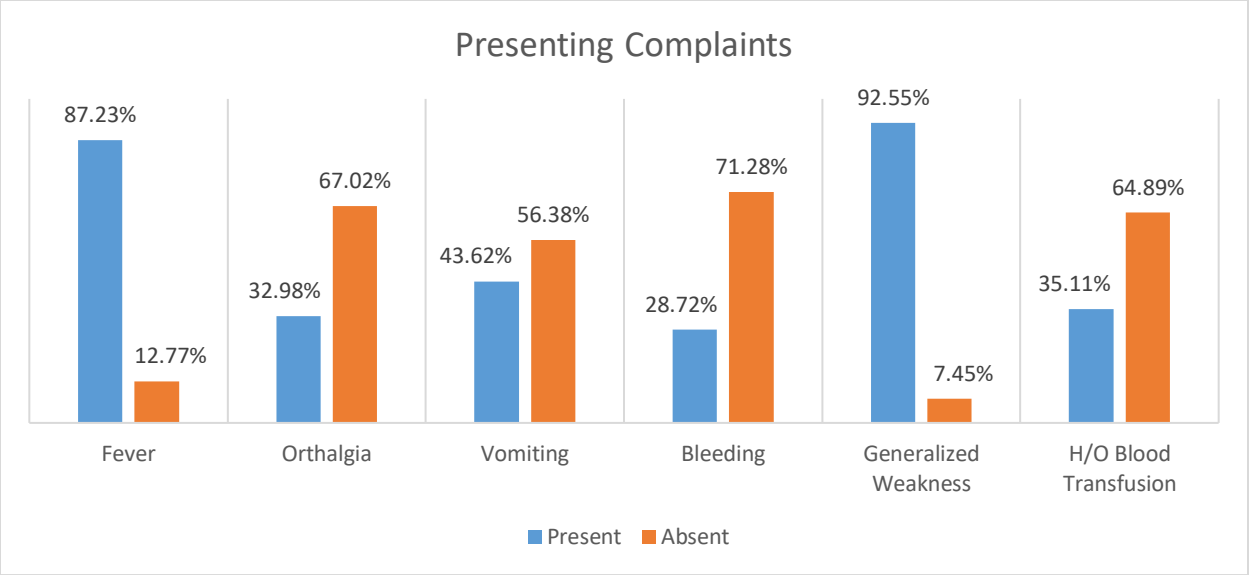
Owing to their vast and multi-factorial origin, the exact pathogenesis of both of these hematopoietic malignancies is not clear, but strong evidence exists that the fms-like tyrosine kinase 3 (FLT3) has an important role to play. **[9]** In addition to identification by molecular characterization, the presence of this genetic aberration can be deduced to some accuracy by clinical hematologic correlates. This research hopes to bring to light, the correlating clinical and hematological features that may serve as potential indicators of the probable presence this mutation, thus helping clinicians in the early detection and prognosis of acute leukemia and resultantly, better induction and consolidation therapy to prevent relapse

METHODOLOGY:

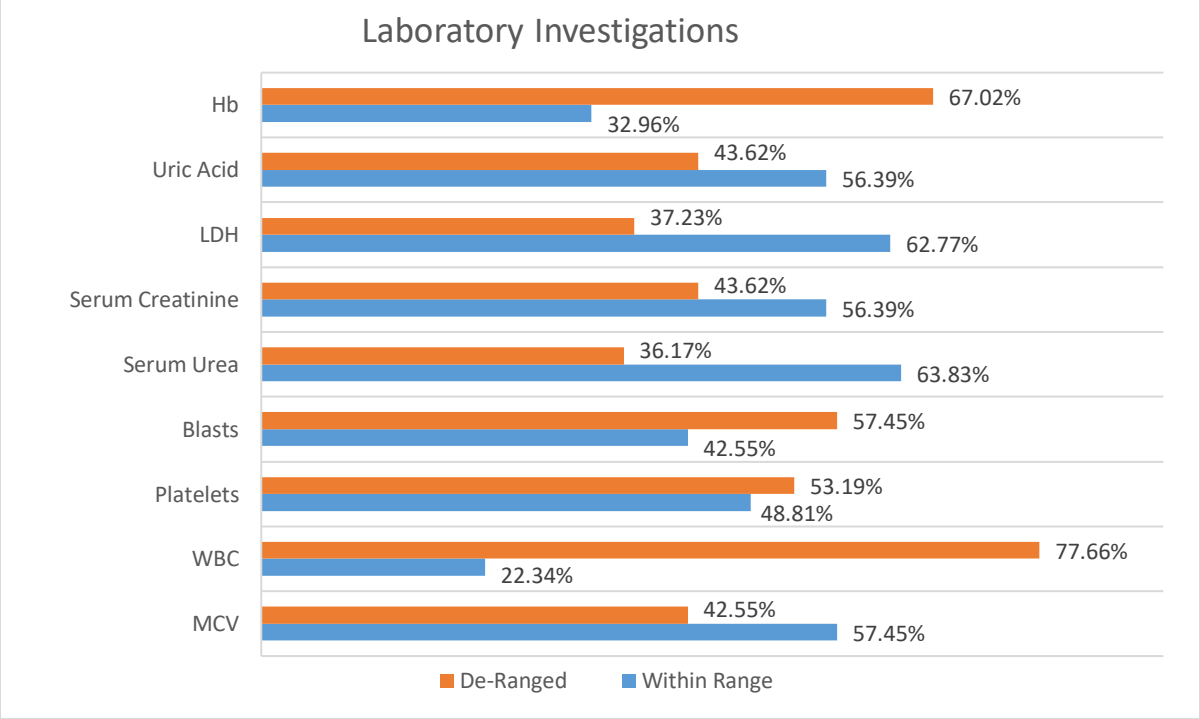
This descriptive analysis was carried out from January 2018 to December 2018 upon a sample of 94 newly diagnosed cases of acute leukemia (chosen via non-probability, consecutive sampling) presenting to the Dept. of Pathology – Liaquat University of Medical & Health Sciences, Jamshoro. Patients meeting the inclusion criteria were enrolled for the study. Data including age, gender, presenting complaint, clinical and laboratory features (e.g. Subtype, Percentage of blasts, Hemoglobin, Total leucocyte count and Platelets count) of each patient were recorded at the time of collection. Detailed laboratory investigations including complete blood count, peripheral film, bone marrow examination, cyto-chemical stain, immunohistochemistry/immune-phenotyping, detection of FLT3 mutation by PCR were also performed. A written informed consent was taken from the study subjects for participation in the study. The data was collected on standard, pre-structured questionnaire by the researcher. Data obtained from laboratory records and patient interviews was recorded into a self-structured questionnaire after taking written informed consent. The data obtained was analyzed using SPSS v. 20.0.

RESULTS:

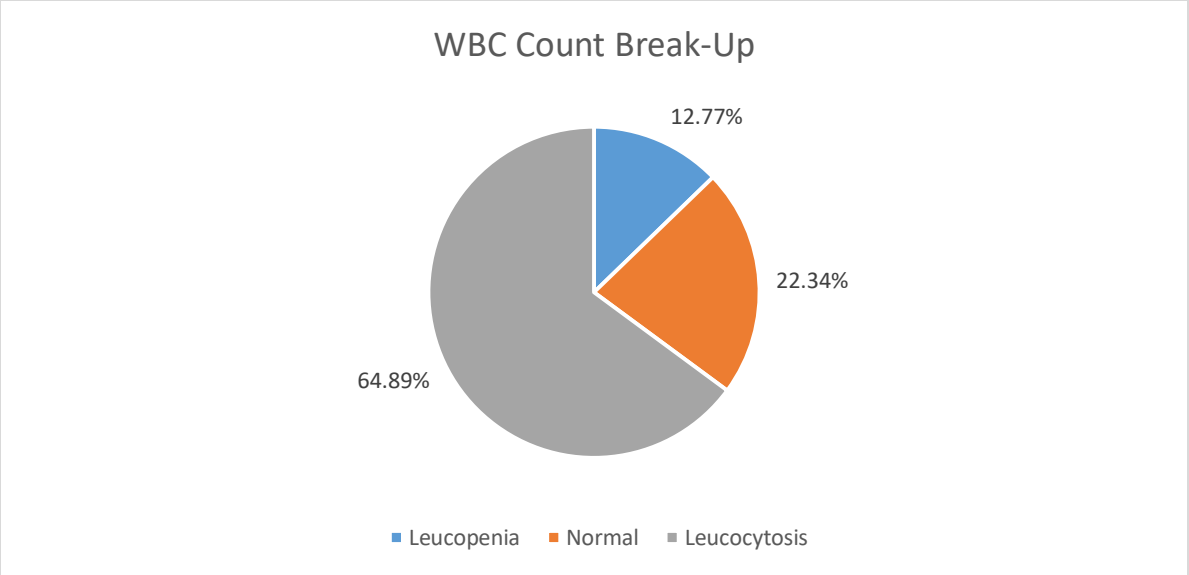
The mean age of the sample stood at 41 years (±19 SD). 59.57% of the sample comprised of males while the remaining 40.43% were females. Among the total of 94 patients studied, polymerase chain reaction demonstrated FLT3 mutations in 6 (11.32%) of 53 AML patients and 2 (4.88%) of 41 ALL patients. The most common presenting complaint reported by the respondents was generalized weakness (92.55%), followed by fever (87.23%). Bleeding was reported least often (28.72%).



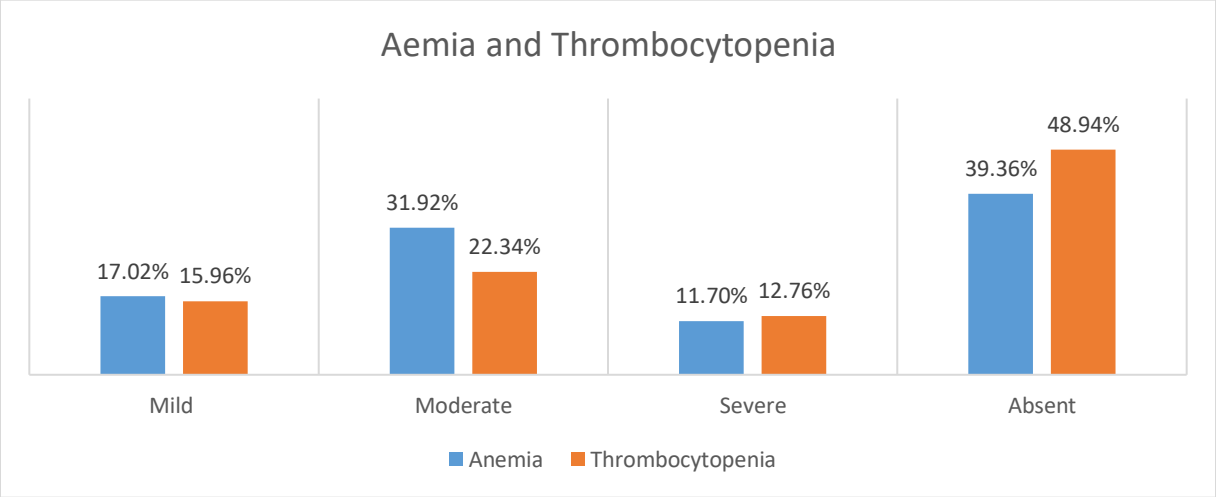
The most mostly commonly deranged laboratory value was WBC count (77.66%), followed by Hemoglobin level (67.02%) with a p value of 0.061 reaching near significant status. The least deranged laboratory value was serum urea (36.17%).



Among the hematological and clinical findings most closely correlated with FLT3 mutation, WBC was the most statistically significant derangement among all hematologic indices studied. (P value < 0.05).WBC was the only statistically significant derangement among all hematologic indices studied. (P value < 0.05).



More patients suffered anemia and thrombocytopenia than not. Anemia was more common than thrombocytopenia, however, neither was statistically significant.



The individual correlation of hematologic & clinical findings is as follows.

Clinical Sign/Symptom	Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia
Fever	47	35
Orthalgia	19	12
Vomiting	15	26
Bleeding	17	10
Generalized Weakness	47	40
H/O Blood Transfusion	12	21

Deranged Laboratory Values	Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia
Haemoglobin	33	30
MCV	29	13
WBC count	43	30
Platelet count	37	13
Blast cells	20	34
Serum Urea	16	18
Serum Creatinine	20	21
LDH	17	18
Uric Acid	19	22

DISCUSSION:

The most common presenting complaint reported by the respondents was generalized weakness (92.55%), followed by fever (87.23%). Bleeding was reported least often (28.72%). This is synonymous with known facts about the condition which report bleeding from the gums, bone pain, fever, frequent infections, frequent or severe nosebleeds, lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin, pale skin and shortness of breath to be among the chief complaints of ALL. AML too has similar symptoms with bruising being more marked than as seen in patients with ALL. **[10, 11]**

Our results also show that the most commonly deranged laboratory value was WBC count (77.66%), followed by Hemoglobin level (67.02%). The least deranged laboratory value was serum urea (36.17%). More patients suffered anemia and thrombocytopenia than not. Anemia was more common than thrombocytopenia, however, neither was statistically significant. Among the hematological and clinical findings most closely correlated with FLT3 mutation, WBC was the most statistically significant.

Existing literature suggests that patients suffering from AML often have an increased WBC count despite having a decreased level of neutrophils in the body. Interestingly enough, consequently the patients have a heightened risk of infection upon hitting a neutrophil counts of < 500 cells/µL or more worryingly, especially after the count falls below 100 cells/µL, which is common in most cases of AML. **[12, 13]**

On the other hand, it reported that the WBC count is greater than 10,000/µL greater than half of all patients with ALL. But here again, the absolute neutrophil count is often low. Another interesting fact is that although the WBC count is markedly high, symptomatology of hyper-leukocytosis is seldom manifested among the patients. Thrombocytopenia. Coagulopathies and anemia (normocytic and normochromic) are the rule. As per the rule, ALL diagnosis is made only after a minimum 30% presence of lymphoblast in the bone marrow aspirates. **[14, 15]**

CONCLUSION:

After careful consideration, it can be concluded that no significant hematological correlates were identified, other than WBC count**.**

REFERENCES:

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015 Mar;65(2):87-108.
2. Chiang AW, Li S, Spahn PN, Richelle A, Kuo CC, Samoudi M, Lewis NE. Modulating carbohydrate–protein interactions through glycoengineering of monoclonal antibodies to impact cancer physiology. Current opinion in structural biology. 2016 Oct 1;40:104-11.
3. Combest AJ, Danford RC, Andrews ER, Simmons A, McAtee P, Reitsma DJ. Overview of the Recent Developments in Chronic Lymphocytic Leukemia, Part 1. Journal of Hematology Oncology Pharmacy. 2016 Jun 1;6(2).
4. Cuervo-Sierra J, Jaime-Pérez JC, Martínez-Hernández RA, García-Sepúlveda RD, Sánchez-Cárdenas M, Gómez-Almaguer D, Ortíz-López R, Villarreal-Villarreal CD, Ruiz-Arguelles GJ, Ruiz-Delgado G, Lutz-Presno J. Prevalence and clinical significance of FLT3 mutation status in acute myeloid leukemia patients: a multicenter study. Archives of medical research. 2016 Apr 1;47(3):172-9.
5. Rodriguez-Galindo C, Friedrich P, Alcasabas P, Antillon F, Banavali S, Castillo L, Israels T, Jeha S, Harif M, Sullivan MJ, Quah TC. Toward the cure of all children with cancer through collaborative efforts: pediatric oncology as a global challenge. Journal of Clinical Oncology. 2015 Sep 20;33(27):3065.
6. Susanna C, Borducchi JH, Mauad V, Del Giglio A, Rodart I, Del Giglio A, Borducchi DM.

Prevalence and Prognostic Impact of FLT3-ITD and NPM1 Mutations: A Cohort of Patients with Acute Myeloid Leukemia from the ABC-SP, Brazil.

7. Meshinchi S, Woods WG, Stirewalt DL, Sweetser DA, Buckley JD, Tjoa TK, Bernstein ID, Radich JP. Prevalence and prognostic significance of Flt3 internal tandem duplication in pediatric acute myeloid leukemia. Blood. 2001 Jan 1;97(1):89-94.
8. Kondo M, Horibe K, Takahashi Y, Matsumoto K, Fukuda M, Inaba J, Kato K, Kojima S, Matsuyama T. Prognostic value of internal tandem duplication of the FLT3 gene in childhood acute myelogenous leukemia. Medical and Pediatric Oncology: The Official Journal of SIOP—International Society of Pediatric Oncology (Societé Internationale d'Oncologie Pédiatrique). 1999 Dec;33(6):525-9.
9. Zwaan CM, Meshinchi S, Radich JP, Veerman AJ, Huismans DR, Munske L, Podleschny M, Hählen K, Pieters R, Zimmermann M, Reinhardt D. FLT3 internal tandem duplication in 234 children with acute myeloid leukemia: prognostic significance and relation to cellular drug resistance. Blood. 2003 Oct 1;102(7):2387-94.
10. Singer AW, Carmichael SL, Selvin S, Fu C, Block G, Metayer C. Maternal diet quality before pregnancy and risk of childhood leukaemia. British Journal of Nutrition. 2016 Oct;116(8):1469-78.
11. Shim KS, Kim MH, Shim CN, Han M, Lim IS, Chae SA, Yun SW, Lee NM, Yi DY, Kim H. Seasonal trends of diagnosis of childhood malignant diseases and viral prevalence in South Korea. Cancer epidemiology. 2017 Dec 1;51:118-24.
12. Wurlitzer K, Burkholder T. Quick Consult: Symptoms Fatigue, Cough, Night Sweats, Gum Bleeding. Emergency Medicine News. 2018 Mar 1;40(3):14-6.
13. Pina-Oviedo S, Torres-Cabala CA, Miranda RN, Tetzlaff MT, Singh S, Rapini RP, Prieto VG, Aung PP. Concomitant cutaneous Langerhans cell hystiocytosis and leukemia cutis. The American Journal of Dermatopathology. 2017 May 1;39(5):388-92.
14. Thapa N, Pham R, Cole C, Meinershagen M, Bowman PW, Ray A. Therapeutic leukocytapheresis in infants and children with leukemia and hyperleukocytosis: A single institution experience. Journal of clinical apheresis. 2018 Jun;33(3):316-23.
15. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood. 2015 May 21;125(21):3246-52.