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### RESEARCH ARTICLE

#### INCIDENCE AND PREVALENCE OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN KASHMIRI POPULACE (NORTH INDIA)

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#### Abstract

**Background:** The most frequent cancer of the childhood is acute lymphoblastic leukaemia (ALL). It is the blood and bone marrow cancer affecting white blood cells. It is caused by errors in the DNA in the bone marrow cells. Our goal was to evaluate the prevalence of ALL in Kashmiri populace.

**Methods:** The study in the hindsight was initiated for ALL patients registered between early 2018 up to late 2019 to investigate its frequency and prevalence.

**Results:** Overall from 74 ALL patients, based on gender, 44 (59%) were males and 30 (41%) were females. Based on age, 53 (72%) were in the age group of  $\leq 18$  years while 21 (28%) were in the age group of  $> 18$ . Based on immunophenotypes 69 (93%) were of Pre B-cell phenotype, 3 (4%) belonged to T-cell phenotype while 2 (3%) were of mixed phenotype. Based on demography, 10 (14%) were from urban areas while as 64 (86%) were from rural areas of Kashmir region.

**Conclusions:** Although the prevalence of ALL in this region is very high, but gender has no significance while age and dwelling has significance on its overall frequency and significance.

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#### Introduction:-

Acute lymphoblastic leukaemia (ALL) is a blood-line lymphoid progenitor cell cancer that develops significant amounts of undefined lymphocytes.<sup>1</sup> It is the most frequent cancer of the childhood. It is caused by errors in the DNA of the bone marrow cells, although the origin is unclear in some circumstances.<sup>2</sup> The development of fresh red blood cells, white blood cells, and platelets has been hindered by excessive production of immature bone marrow lymphocytes.<sup>1</sup> The indications and manifestations of ALL vary<sup>3</sup> and usually include anemia, bloody nose, bone pain, breathlessness, bruising, contusions, common infections, drowsiness, enlarged liver and spleen lymph nodes, fatigue, fever and infection, gum bleeding, headache, joint pain caused by the spread of blast cells, lower limb and belly swelling, lethargy, loss of weight and appetite, night sweats, rigidity of the neck,<sup>4</sup> or paralysis of the cranial nerve<sup>5</sup> (CNS involvement), paleness, skin rashes/red spots due to low platelet count, shortness of breath, vomiting, weakness and tiredness. ALL develops quickly as acute leukemia and if untreated may become lethal in a matter of weeks or months.<sup>6</sup> During the progression of B and T cell differentiation, any genetic insult that block

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precursor B or T cell differentiation and drives their deviant proliferation and survival may cause different health disorders including ALL. Of all the ALL cases, B-ALL, which is characterized by hard line malignancy of small to medium size precursor B cells comprises approximately 80-85% as compared to T-ALL.<sup>1</sup> Like other tumors, ALL outcome from the amassing of genomic abnormalities that it affects normal control of cellular growth.

Down syndrome, Li-Fraumeni syndrome or type 1 neurofibromatosis may be some of the genetic risk factors.<sup>1</sup> Though chemotherapy or selective medicines that directly destroy cancer cells are used as treatments, but exposure to radiation or previous chemotherapy may be some of the environmental risk factors.<sup>1</sup> There is contradictory evidence about the role of electromagnetic waves or pesticides in the development of ALL.<sup>7, 8</sup> Some theorize that a typical infection may cause an unexpected immune reaction therefore trigger its development.<sup>7</sup> While others speculate that multiple genetic mutations result in rapid cell division thus are the basic underlying mechanisms.<sup>2</sup>

Typically, diagnosis is dependent on blood tests and analysis of the bone marrow.<sup>9</sup> Initial symptoms, especially in infants, can be ambiguously defined. More than 50% of children with leukaemia have one or more of these five traits: hepatomegaly (64%), splenomegaly (61%), pale skin (54%), fever (53%) and bruising (52%).<sup>10</sup> Recurring infections, sluggish feelings, leg or arm pain and swollen lymph nodes may also become common. Other symptoms are also often present, such as fever, night sweats and weight loss. Symptoms such as cranial neuropathies attributable to meningeal invasion of the central nervous system (CNS) were detected in 10% of adults and less than 5% of the infants, in particular mature B-cell ALL (Burkitt leukemia) at the initial diagnosis.<sup>11</sup>

ALL is initially treated with chemotherapy to cause remission. This is often usually supplemented over several years by more chemotherapy.<sup>2</sup> Treatment also commonly involves intrathecal chemotherapy, as systemic chemotherapy may have little access into the central nervous system, a popular site for the regeneration of acute lymphoblastic leukaemia.<sup>12, 13</sup> Radiation therapy can also be used when the disease is spread towards the brain. Transplantation of stem cells may be used as the condition resurges after conventional therapy. More therapies are being employed and investigated as of now.<sup>2</sup>

According to gender, women more likely fare better than men. In general, the African-Americans, Asians and Hispanics are less likely to develop leukemia than caucasians. ALL in particular happens more frequently in Caucasians, Hispanics and Latin Americans than in Africans.<sup>14, 15</sup> But they much more likely have positive prognosis than their non-caucasian counterparts. In the United States, ALL is most prevalent in children of Caucasian (36 cases/million) and Hispanic (41 cases/million) descent in comparison to children of African descent (15 cases/million).<sup>16</sup> It is more likely that children between the ages of 1 and 10 though develop ALL but in the long run get healed. The most plausible outcome of chromosome defects (e.g., Philadelphia chromosome) in older adults that make the treatment management harder with worse prognosis. Older individuals can also have underlying co-morbidity that make ALL therapy much harder to tolerate. At diagnosis, the number of White Blood Cells >30,000 (B-ALL) or >100,000 (T-ALL) is concomitant with worse outcomes. Cancer spreads to the CNS (brain or spinal cord) have worse implications. Person's initial recovery response and longer time needed to achieve full remission which is >4 weeks. Patients with genetic defects such as Down syndrome and other chromosomal anomalies may have a different response and remission rate.<sup>17</sup>

In 2015, ALL affected approximately 876,000 people in the world and led to approximately 111,000 deaths.<sup>18, 19</sup> This is the most prevalent cause of cancer and death in children in the United States.<sup>2</sup> It is observed in both adults and children, but in children especially between the ages of 3 and 7 highest frequencies of ALL is observed.<sup>4, 20</sup> It is believed to affect 1 in 1500 children.<sup>21</sup> Around 75% of cases appear before 6 and a secondary spike after 40 years of age.<sup>22</sup> Children survived for a median period of 3 months, primarily due to either infection or bleedings, before chemotherapy regimen and hematopoietic stem cell transplant were introduced. ALL has been the first cancer to be cured.<sup>23</sup> The prognosis of childhood leukaemia after chemotherapy has been significantly improved and the likelihood of complete recovery of children with ALL after 4 weeks is projected at 95% after initial therapy. In developing nations, paediatric ALL patients have a 5-year survival rate of more than 80%. 60-80% of people receiving induced chemotherapy are expected to have full remission after 4 weeks and those over 70 years are estimated to have a cure rate of 5%.<sup>22</sup> Infant survival rose to 90% in 2015 from less than 10% in the 1960s.<sup>2</sup> For babies survival still remains less (50%)<sup>24</sup> and adults, the survival rate is even lesser (35%).<sup>25</sup> The National Cancer Intelligence Network (NCIN) reports that after initial diagnosis 70% people with ALL typically live for 5 years or longer.

ALL presently occurs in  $\sim 1.7/10^6$  /year with the broad age profiles of those affected. ALL is the most prevalent childhood disease, represented about 20% of adults and 80% of childhood leukaemias.<sup>26</sup> Although a long-term, comprehensive response towards treatment is seen in 80% to 90% of children,<sup>27</sup> it still remains the leading cause of childhood deaths.<sup>28</sup> 85% of the cases among both males and females are of B cell passages having the same number of cases. The remaining 15% are male predominant T-cell lineage. Here in this region (J&K, India), ALL ranks 5<sup>th</sup> among common cancers occurring at a frequency of 9.9% with male: female ratio of 1:1. The average incidence of leukemia in our valley is  $5.8/10^5$ /year with highest incidence in Acute Lymphoblastic Leukemia.

### Methods:-

The present study was carried out in Advanced Centre for Human Genetics at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Srinagar, India from the beginning of 2018 till the end of 2019. For frequency and prevalence studies, 74 cases diagnosed with ALL were enrolled from Department of Pediatric Oncology and Clinical Hematology. The records were screened retrospectively for patients with ALL. Patients from outside the valley of Kashmir were excluded from the study. Emphasis was laid to determine the various factors responsible for ALL which primarily included age, smoking status, use of pesticides, family history and immunological parameters. The research was approved by the local Institutional Ethical Committee of Sher-i-Kashmir Institute of Medical Sciences. The patient's history was evaluated thoroughly and written informed consents were obtained from either the patients themselves or their guardians. The admission records available were scrutinised and reviewed for detailed history. An in-house proforma was used to collect information on demographic data and risk factors. Every parameter such as blast percentage, hemoglobin, WBC and platelet count was taken into consideration.

### Results:-

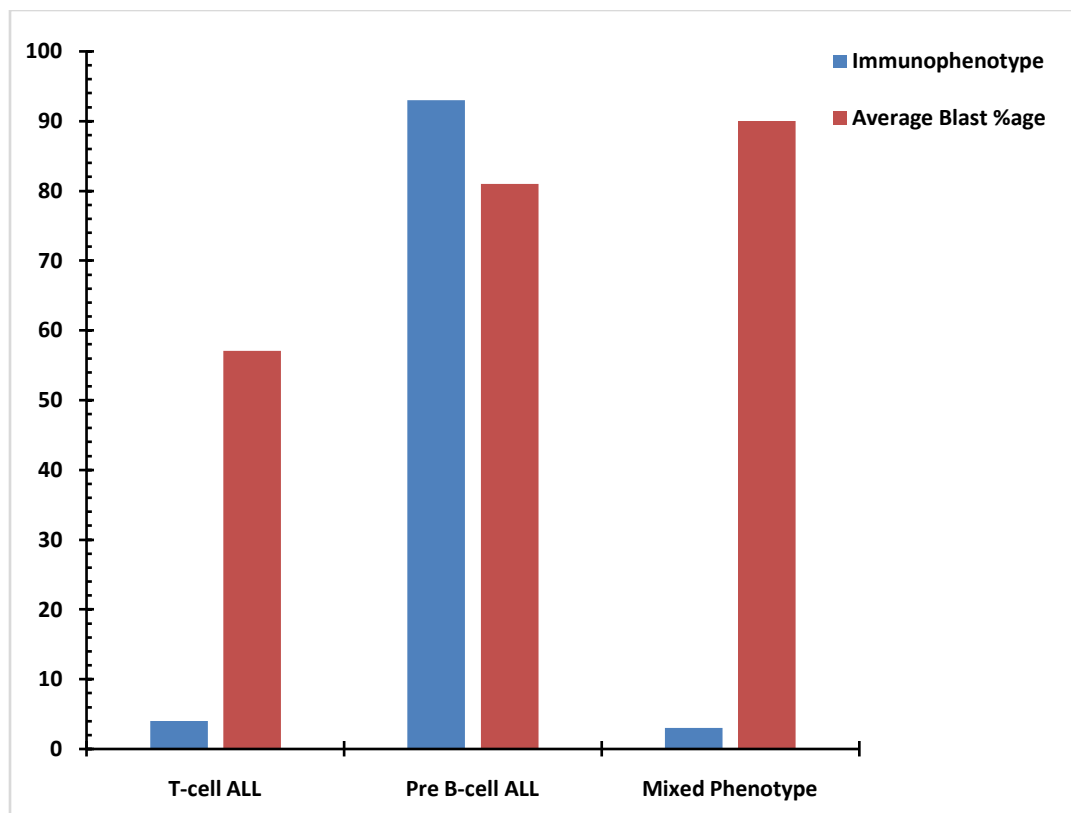
In our study we included a total of 74 cases of ALL patients from Kashmir region who had been diagnosed for the said disease in the Department of Paediatric Oncology and Department of Clinical Haematology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS). Various parameters were taken into study like age, smoking status, and use of pesticides, family history and immunological parameters which can be the risk factors for the development of ALL.

Among the 74 ALL patients, 53 were children (72%) whereas 21 were adult (28%). According to the gender, ALL was common among males 44 (59%) than in females 30 (42%). As far as age is concerned, regardless of the gender, 53 (72%) were in the age group of  $\leq 18$  years while 21 (28%) were in the age group of  $> 18$  signifying that lower age groups have a higher chance of developing ALL. Based on demography, 10 (14%) were from urban areas while as 64 (86%) were from rural areas of Kashmir region indicating that there may be some environmental risks which can be one of the links leading to the development of ALL (Table 1).

Based on clinical parameters, 56 (76%) of the ALL patients had WBC count of  $< 10 \times 10^3/\mu\text{L}$  while 18 (24%) of the ALL patients had WBC count of  $> 10 \times 10^3/\mu\text{L}$  suggesting that most of the ALL patients are presented with high WBC counts. Based on platelet count, 57 (77%) of the ALL patients had platelet count of  $> 150 \text{ mm}^3/\mu\text{L}$  while 17 (23%) of the ALL patients had platelet count of  $< 150 \text{ mm}^3/\mu\text{L}$  suggesting that the high platelets as WBCs is also observed in most of the ALL patients (Table 1). Based on immunophenotypes 69 (93%) were of Pre B-cell phenotype, 3 (4%) belonged to T-cell phenotype while 2 (3%) were of mixed phenotype which depicts that in Kashmiri population there is a predominance of Pre B-cell ALL phenotype (Graph 1)

Characteristics	ALL Cases, n= 74	(%)
<b>Gender</b>		
Male	44	(59%)
Female	30	(41%)
<b>Age</b>		
≤18 years	53	(72%)
>18years	21	(28%)
<b>WBC counts (<math>10^3/\mu\text{l}</math>)</b>		
<10	56	(76%)
≥10	18	(24%)
<b>Platelet count at base line - cells/mm<sup>3</sup></b>		
<150	17	(23%)
≥150	57	(77%)
<b>Immunophenotypes</b>		
T-ALL	03	(04%)
precursor-B ALL	69	(93%)
Mixed phenotype	02	(03%)
<b>Average % Blast</b>		
T-ALL	03	57%
precursor-B ALL	69	81%
Mixed phenotype	02	90%
<b>Dwelling</b>		
Urban	10	(14%)
Rural	64	(86%)

**Table 1:-** Clinico-pathological parameters of Acute lymphoblastic leukemia Patients.



**Graph 1:-** Pattern of Average Blast percentage among different ALL Immunophenotypes.

### Discussion:-

ALL is mainly the most common pediatric cancer that has comparably better survival rate if treated and managed properly with the background knowledge of clinical parameters and genetic molecular profile. Prospects of successful treatment is associated numerous factors like age, gender, WBC count, French-American-British (FAB) classification, and a lot of other factors as well. As per a detailed study by Arshad et al (2011)<sup>29</sup> in valley of Kashmir, leukemia ranks 5<sup>th</sup> among common cancers occurring at a frequency of 9.9% with male: female ratio of 1:1. The average incidence of leukemia in our valley is 5.8/10<sup>5</sup>/year with highest incidence in Acute Lymphoblastic Leukemia. The common age group found to be affected is 2 to 10 years of age. In this study we have discussed multiple features and risk factors of ALL and compared characteristics of ALL patients from Kashmir region. The data covered most aspects of ALL, its incidence and prevalence in addition to factors which are correlated with overall diagnosis and prognosis such as gender, ALL immunophenotypes, and WBC as well as platelet counts.

Leukemia has been seen to be one of the most significant causes of infant deaths, however over the past decades significant progress has been made in the treatment of infant cancers.<sup>30</sup> Just 10% of children's tumours were clinically and epidemiologically differentiated and in 90% of the cases no clear aetiology has been established. Infant leukaemia and other cancers seem to be multifactorial diseases, in which environmental and genetic causes play significant role.<sup>31</sup> Tiredness, fever, bleeding, chest pain and splenomegaly is often associated with leukaemia. Leukemia is also one of the common causes of deaths in children. Finding beneficial factors can contribute to early diagnosis and effective treatment of patients and to the improvement of screening procedures for that patients.<sup>32</sup>

The most prevalent findings in many patients compared to many experiments were systemic complications, typically severe anaemia, erratic platelet counts, lymphadenopathy and hepato-splenomegaly. ALL has several unfavourable prognostic variables, such as high WBC counts, high platelet counts and lymphadenopathy.<sup>33</sup> In the present study, 56 (76%) of the ALL patients had WBC count of  $<10 \times 10^3/\mu\text{L}$  while 18 (24%) of the ALL patients had WBC count of  $>10 \times 10^3/\mu\text{L}$  suggesting that most of the ALL patients are presented with high WBC counts. In our study, 57 (77%) of the ALL patients had platelet count of  $>150 \text{ mm}^3/\mu\text{L}$  while 17 (23%) of the ALL patients had platelet count of  $<150 \text{ mm}^3/\mu\text{L}$  suggesting that the high platelets like WBCs is also observed in most of the ALL patients. In most studies, only few patients were diagnosed with normal levels of these variables but almost all patients were having abnormal levels of these variables.<sup>34</sup>

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