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Epidemiological and Clinical Correlates of Leukemia Ascertained in a Multiethnic Cohort of Pakistan

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ABSTRACT

Leukemia is one of the most prevalent cancers among pediatric malignancies and causes huge economic burden. In this case-control study epidemiological, environmental, life-style related risk factors and phenotypic characteristics of leukemia subtypes were investigated in Pakistani population. A total of 1500 subjects, including 616 patients and 884 controls were recruited through a retrospective cross-sectional sampling design. Descriptive summaries were generated, and risk factors were analyzed through logistic regression. We identified Pathan ethnicity (OR=2.85; 95%CI=2.29-3.54), no formal education (OR=3.36; 95%CI=2.62-4.32), poor diet (OR=2.34; 95%CI=1.79-3.06), lower BMI (OR=1.95; 95%CI=1.50-2.60), parental consanguinity (OR=2.13; 95%CI=1.67-2.71), positive family history (OR=4.24; 95%CI=2.18-8.26), rural residential setup (OR=2.93; 95%CI=2.10-4.10), drinking of groundwater (OR=2.25; 95%CI=1.6479-3.0964), wooden fuel (OR= 3.97; 95%CI=3.14-5.01), carbonated drinks (OR=1.25, 95%CI=1.00-1.57) and tobacco usage (OR=1.57, 95%CI=1.24-1.98) as significant risk factors for leukemia. However, odds ratios were significantly lower for patients using microwave oven (OR=0.25; 95%CI=0.18-0.35), and perfumes (OR=0.42; 95%CI=0.33-0.53). Males exhibit an increased risk for lymphoid leukemia as compared to myeloid leukemia (OR=1.97; 95%CI=1.38-2.80). Paraclinical parameters indicated that 71% of the cases had >50% of blast cells. Leukocytosis (OR= 9.06; 95% CI=6.46-12.71), anemia (OR= 15.84; 95% CI=11.84-21.21), low hemoglobin (OR=8.11; 95% CI=6.35-10.37), thrombocytopenia (OR=32.40; 95% CI=21.57-48.68), lymphocytosis (OR= 3.41; 95% CI=2.55-4.57), and neutropenia (OR=7.32; 95% CI=5.59-9.60) had significantly higher odd ratio for leukemia patients. Leukemia risk factors are mainly relevant to exposure due to rural residence, poor lifestyle, and family history of the disease. The disease incidence can be minimized by designing and implementing risk mitigation strategies.

INTRODUCTION

Leukemia is a heterogeneous group of clonal hematologic malignancies characterized by the abnormal proliferation of hematopoietic cells interrupting the normal function of blood and bone marrow. General manifestations of leukemia include fever or chills, dyspnea, persistent fatigue, weakness, recurrent infections, weight loss, swollen lymph nodes, enlarged liver or spleen, and bruising (Castro *et al*., 2015; Louvigne *et al*., 2020). It is subdivided into acute lymphoblastic

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leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML) as major divisions. Leukemia is the most common type of cancer in children (Ferlay *et al*., 2015). Incidence of leukemia subtypes varies according to geography, age, gender, and race, and exhibits different clinical features, treatment response, relapse kinetics, and relapse sites (Belurkar *et al*., 2013). Leukemia accounts for numerous morbidities and mortalities worldwide. In 2015, there were 606,000 estimated new cases of leukemia worldwide and 353,000 deaths (Fitzmaurice *et al*., 2017). In general, the global burden of leukemia increased slightly from 1990 to 2017 (Lin *et al*., 2021). In 2020, there were 60,530 estimated morbidities and 23100 mortalities due to leukemia in the US, alone (Siegel *et al*., 2021). Mortality due to leukemia has descended recently, but leukemia is still a highly prevalent disease that leads to considerable disability and increased economic costs. It not only results in a major personal burden but also affects families and the economic structures of countries.

In Pakistan, leukemia is one of the recurrent cancers in the general population and is the second most prevalent cancer among pediatric malignancies (Shahid *et al*., 2021). In Pakistan, leukemia patients have a poor quality of life in Pakistan (Malik *et al*., 2021). Further, weak socioeconomic status, lower literacy rate, and socially stigmatized situation are directly or indirectly adding up to the disease burden (Khokhar *et al*., 2020). Being a lower economic country, Pakistan is facing major problems in the health sector. There is a gross deficit of oncological services, and every oncologist deals with 1300-1500 patients annually, even in the country's developed province, Punjab (Khokhar *et al*., 2020). Lack of qualified, trained oncologists, poor healthcare infrastructure, limited access to healthcare facilities, and deficiency of equipment for diagnosis are the major factors affecting the control and prevention of blood cancers in Pakistan.

The unavailability of countrywide leukemia prevalence statistics, absence of any planning and prevention strategies; and lack of educational and research programs are making the situation intimidating. The financial burden of leukemia care is huge and overwhelming due to factors like unstable economy/currency, huge unemployment, and the import of instruments and drugs for leukemia diagnosis and treatment in Pakistan. Previous literature demonstrates the existence of significantly worse survival among economically disadvantaged patients (Acharya *et al*., 2016). Therefore, it is highly desired to focus on leukemia prevention as the healthcare resources of the country are limited.

Epidemiological integrated transdisciplinary research is needed for estimation of the actual leukemia burden in Pakistan, identification of contributing risk factors, and designing feasible prevention strategies for leukemia unique to the Pakistani population. In this context, the present epidemiological case-control study was designed to investigate the bio-demographic attributes of leukemia patients and to identify potential risk factors associated with leukemia in the multiethnic Pakistani population.

MATERIALS AND METHODS

Patients of all gender, age group, and ethnicities from the Pakistani population suffering from any subtype of leukemia, both newly diagnosed or actively on treatment, were included in the study without bias, While Patients of other closely related cancers i.e., lymphoma, myeloproliferative neoplasms (CML exempted), and off-treatment leukemia patients were excluded from the study. For comparison, age, gender, and ethnicity matched healthy controls, belonging to similar areas, environmental conditions, and socio-economic status were randomly collected during 2017-2020. About 70% of the eligible controls consented to participate in the study, the hesitant controls were majorly comprised of children. The detailed medical records of the patients were acquired and data on clinical diagnosis, demography, lifestyle, and risk factors were obtained. Data were systematically collected by trained researchers through direct onsite interviews (conducted for each patient individually as they get recruited for the study during the sampling span, to minimize the time lag between the diagnosis and interview) with the participants/guardians (children), on a mixed questionnaire, containing both open-ended and closed-ended questions based on the type of variable in question. The definitions of the demographic variables were obtained from Pakistan Demographic and Health Survey (Nips, 2019).

Sample and study parameters

The patients and controls were categorized into five groups based on their age; infants (<1 year), preschoolers (1.1-5 years), children (5.1-15 years), adolescents, and young adults (AYAs; 15.1-39 years), and aged (39.1 and>). The risk factors considered for this study were weight, diet, education, parental consanguinity, family history of cancer, area, drinking water source, fuel type used in the household (wood or natural gas), use of carbonated drink, perfume use, and tobacco use (Supplementary Tables I and II).

Body mass index (BMI) was derived from the height and weight (patients weights at the time of diagnosis were considered) taken during the sampling. Age and gender-specific indices were used for BMI/percentile calculation.

According to international standards, a child's weight below the 5th percentile, 6-85 percentile, and >85 percentile were considered as underweight, normal, and overweight respectively. In adults, individuals with BMI <18.5kg/m2 were considered underweight, with BMI of 18.5kg/m2-24.9kg/m2 as normal, while BMI >24.9kg/m2 were considered overweight. Tobacco use (Active/ parental: in case of children) included both smoking (cigarette; active/passive) and smokeless (pan, baerri, powdered tobacco) forms. Diet is categorized into standard and poor diet. A standard diet includes an intake of fruit, vegetables, legumes, nuts, whole grains, and meat. A poor diet is a diet lacking one or more of the food groups (WHO, 2019). Participants in the study, who were unable to consume any major group of bio-nutrients like proteins or carbohydrates, continuously for longer than WHO recommended durations were considered to have a poor diet. For each patient, a detailed pedigree was constructed. Parental marriage types up to the second cousin with inbreeding coefficient of F=0.0156 were considered consanguineous. Individuals who obtained some level (primary; 5 years, secondary; 10 years, graduation; 14 years, masters; 16 years, and so on) of formal education were considered educated while children below the age of 5 years were placed in the inadmissible category and individuals who have not obtained any form of school education were placed in no formal education category.

Hematological fluctuations of blood cellular count for all study participants were also compared in this study. Hematologic parameters consist of white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb), platelets, lymphocyte%, and neutrophils%. All the parameters were categorized into increment, normal, and decrement categories according to the employed reference standard level for children, adults, males, and females, in the country (Supplementary Table III).

Statistical analysis

Descriptive statistical methods were used to summarize the clinical characteristics, demographic, and lifestyle-related factors of the study participants. We determined potential demographic, lifestyle, and clinical risk factors by using univariate logistic regression, comparing each parameter between patients and controls. The comparison was performed on three distinct levels: (i). compared overall numbers of patients and controls against each variable (Supplementary Table IV and V), (ii). Categorizing both patients and controls in age groups (<1, 1.1-5, 5.1-15, 15.1-39, >39 years; Table I) and then performed a group-to-group comparison of patients and controls against each variable (Supplementary Table VI), (iii). To identify the high-risk age group within the patients, the age groups within the patients cohort were compared with one another (Supplementary Table VII). In age group-wise comparison, a group vs a group and a group vs all other groups (additive model) assessment was implied separately for every variable, in both (ii) and (iii) levels of comparison. The percentage of the missing data was excluded in the respective statistical analysis to avoid its interference with the assessment. Odds ratios with 95% confidence intervals were calculated to identify the presence and strength of the association. A p-value of $\leq$ 0.05 was considered statistically significant.

RESULTS

Sample characteristics

A total of 1500 samples were collected, which comprised 616 patients and 884 age, gender, and ethnicity-matched controls for comparison. Detailed clinical and paraclinical reports were obtained for 92% of the patients remaining were not available. Among all, the data of 594 patients and 884 controls were included in the analysis, and 22 patients were excluded due to incomplete data.

Table I. Type-wise distribution of leukemia patients.

Age groups (Years)	Patients								Controls	Net Total	
	Leukemia subtype				Disease origin		Disease type		Total	Total	Overall number
	ALL	CLL	AML	CML	Lymphoid	Myeloid	Acute	Chronic			
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N
<1	6 (1.01)	0 (0)	0 (0)	1 (0.17)	6 (1.01)	1 (0.17)	6 (1.01)	1 (0.17)	7 (1.18)	10 (1.13)	17
1.1-5	108 (18.18)	0 (0)	6 (1.01)	2 (0.34)	108 (18.18)	8 (1.35)	114 (19.19)	2 (0.34)	116 (19.53)	74 (8.37)	190
5.1-15	150 (25.25)	0 (0)	18 (3.03)	3 (0.51)	150 (25.25)	21 (3.54)	168 (28.28)	3 (0.51)	171 (28.79)	117 (13.24)	288
15.1-39	72 (12.12)	1 (0.17)	31 (5.22)	44 (7.41)	73 (12.29)	75 (12.63)	103 (17.34)	45 (7.58)	148 (24.92)	503 (56.9)	651
39.1 and >	16 (2.69)	29 (4.88)	24 (4.04)	83 (13.97)	45 (7.58)	107 (18.01)	40 (6.73)	112 (18.86)	152 (25.59)	180 (20.36)	332
Total	352 (59.26)	30 (5.05)	79 (13.3)	133 (22.39)	382 (64.31)	212 (35.69)	431 (72.56)	163 (27.44)	594 (100)	884 (100)	1478

For abbreviations, see Figure 1.

Among the total 616 patients, 67% were male and 33% were female. An overall male to female ratio of 2:1 has been observed in leukemia patients. The highest occurrence of leukemia was seen in children 5 to 15 years of age (28.79%) and individuals >39 years old of age (25.59%). The details of all the variables included in the study are given in Supplementary Tables I, II, and III.

Leukemia subtypes

In type-wise distribution, ALL was the most prevalent group (59%), affecting children mostly, followed by CML (22%) affecting the AYAs age group. Among ALL, 73% of the patients were having acute (majorly consisting of children and Adolescent and young adults (AYAs)) and 26 % were suffering from chronic leukemia (common in aged individuals). Similarly, 65% were having leukemias of lymphoid origin, while 35% were having myeloid leukemia (Table I, Fig. 1).

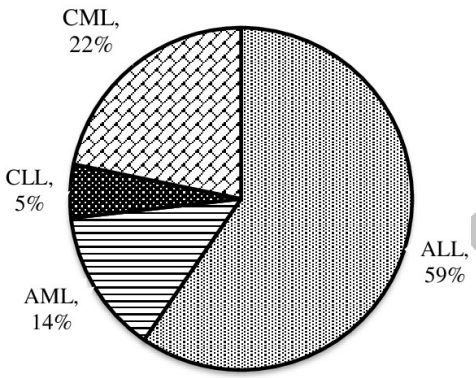

Fig. 1. Percentage distribution of leukemia subtypes in Pakistani population, Acute lymphoblastic leukemia (ALL) was the most recurrent leukemia subtype, seen frequently in children (1-15 years). Myeloid leukemias (chronic myeloid leukemia; CML, acute myeloid leukemia; AML) were frequently seen in adults (15.1 – 39 and > 39 years), while chronic lymphocytic leukemia (CLL) was the least occurring leukemia subtype and observed only in adults (greater than 39 years old) in the study population.

Gender, ethnicity, education, and leukemia risk

In the present study, the male gender has about a 2-fold increased risk for lymphoid leukemia as compared to myeloid leukemia (OR=1.97, 95%CI 1.38-2.80). AYAs have a 2.31-fold higher risk for myeloid leukemia compared to all other age groups of patients (OR=2.31, 95%CI 1.58-3.38). Age group >39.1 has a 21.46-fold high risk for chronic leukemia as compared to all other age groups of patients (OR= 21.46; 95%CI=13.49-34.14) (Supplementary Table VII, Fig. 5). The risk for Pathan ethnicity has a 2.8-fold increased risk as compared to controls (OR=2.85; 95% CI=2.29-3.54). The risk of no education in leukemia patients has a significantly increased risk as compared to controls (OR=3.36; 95% CI=2.62-4.32; Supplementary Table IV, Fig. 2).

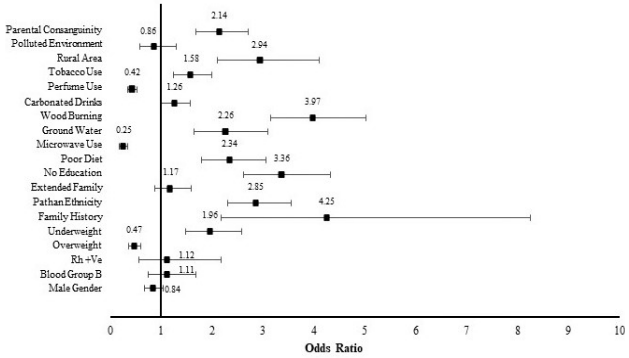

Fig. 2. Odds ratios were calculated comparing the exposure of risk factor to patients and controls (CI 95%, p*= 0.05). It is indicated that lower BMI (ref. normal and higher BMI), poor diet (ref. standard BMI), all forms of tobacco use (ref. no use), consanguineous parental union (non-consanguineous parental union), family history of leukemia and solid cancers (ref. no family history), lack of basic education (ref. educated) and hailing to Pathan ethnicity (ref. other ethnicities additively) were high risks variables significantly associated to leukemia. In lifestyle related factors, wood burning, consumption of unprocessed ground water for drinking purposes, living in a residential rural set up were found to increase leukemia risk significantly and use of carbonated drinks was only observed to cause a slight but significant risk for leukemia; However, wearing perfume and microwave use has been observed to have protective effect for leukemia risk. The reference used for above factors were gas burning, water from all other sources, urban residential set up, no consumption of carbonated drinks, no use of perfume and no use of microwave, respectively. No significant risk-based association was noticed for extended family type, blood group B, Rh +ve, and gender in the studied population for leukemia patients in comparison to controls, taking nuclear family, all other blood groups than B, Rh -ve and female gender as reference.

Diet, weight, and leukemia risk

Overall, patients with a poor diet have a 2.34-fold higher risk for leukemia as compared to controls (OR=2.34; 95% CI=1.79-3.06; Supplementary Table IV, Fig. 2), while patients in the age group 5.1-15 with a poor diet face a higher risk for leukemia in comparison to matched controls (OR=2.70; 95% CI=1.55-4.59; Supplementary Table VI, Fig. 4).

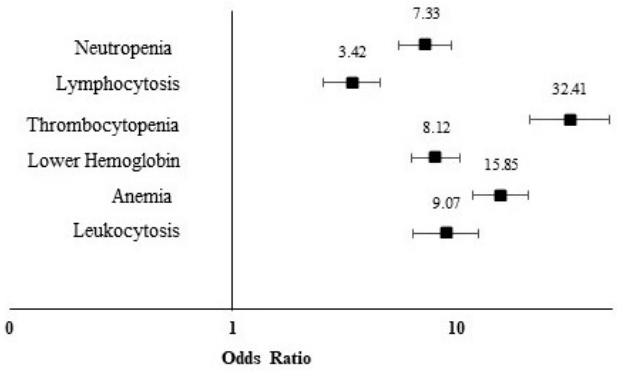

Fig. 3. Leukocytosis (ref. additive model; normal count, leukocytopenia), lymphocytosis (ref. additive model; normal count, lymphocytopenia), are significantly associated to leukemia patients in comparison to age and gender matched controls (CI 95%, p* = 0.05). Also, on contrary, anemia (ref. additive model; normal count, erythrocytosis), hemoglobin (ref. additive model; normal and higher level), and thrombocytopenia (ref. additive model; normal count, thrombocytosis), were highly significant in leukemia patients.

Lower BMI significantly increased the risk for leukemia in this study as compared to controls (OR=1.95; 95% CI=1.50-2.60; Fig. 2). Pre-schoolers (1.1-5 years) with lower BMI have a significant, 7.9-fold higher risk for leukemia, as compared to patients in the age group 5.1-15 years (OR=7.92; 95% CI=3.71-16.88) and 28.37-fold higher risk in comparison to the additive risk of all other age groups (OR=28.37; 95% CI=3.74-58.57) of the patients (Supplementary Table VII, Figs. 5, 6).

Consanguinity and family history as a risk factor for leukemia

Patients with the parental consanguineous union had a 2-fold higher, significant risk for leukemia as compared to controls (OR=2.13; 95% CI=1.67-2.71; Supplementary Table IV, Fig. 2). Particularly, patients in the age group 5.1-15 with parental consanguinity have been observed to have an increased risk for leukemia in comparison to controls (OR= 1.6, 95% CI=1.03-2.39: Supplementary Table VI, Fig. 4). In this study, the patients with a family history of leukemia/solid cancers, have 4-fold increased risk for leukemia as compared to controls (OR= 4.24, 95% CI=2.18-8.26: Supplementary Table IV, Fig. 2).

Lifestyle and residential risk factors

In this study, patients living in the rural residential setup have a 2.9-fold increase, a significant risk for leukemia as compared to controls (OR=2.93, 95% CI=2.10-4. 10; Supplementary Table IV, Fig. 2). The leukemia patients in the age group 5.1-15, residing in a rural area, have 1.7-fold higher risk (OR=2.70; 95% CI=1.82-4.02), as compared to age-matched controls. A similar relationship was shown by the preschoolers (1.1-5 years) (OR=1.92; 95% CI=1.23-2.99). However, no such association was identified in adult patients (Supplementary Table VI, Fig. 4).

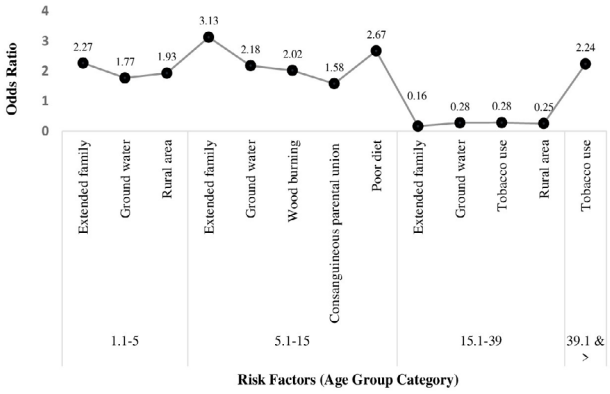

Fig. 4. Odds ratios calculated to identify age group related risk factors for patients comparing to controls (CI 95%, p* = 0.05), indicated that although, extended family type was over all nonsignificant, but is a significant risk factor for children below age of 5 years with leukemia (ref. extended family type in remaining age groups), along with ground water consumption (ref. ground water consumption in all remaining age groups) and rural residential set up (ref. rural residential set up in remaining age groups). For patients of age 5.1-15 years old, extended family, ground water, wood burning (ref. wood burning in remaining age groups) as domestic fuel, consanguineous parental unions (ref. consanguineous parental unions in all remaining age groups), and poor diet (ref. poor diet in remaining age groups) were associated with high risk of leukemia. For patient older than 39 years of age, tobacco use (ref. tobacco use in remaining age groups) was significantly associated compared to controls; However, the for the Adolescents and young adults (AYAs; 15.1-39 years), designated as a unique group in oncology, although being a huge group in present study, the pattern was changed. As risk factors for other age groups, e.g., extended family, ground water, tobacco use, and rural residency are exhibiting protective effects when compared to age matched controls. The occurrence of the respective risk factor in all of the remaining age groups was treated as reference in each case.

Consuming groundwater as a primary drinking water source has been associated with an increased risk for leukemia in this study (OR=2.25; 95% CI=1.6479-3.0964; Supplementary Table IV, Fig. 2). Particularly, the risk is significant for children (OR= 2.17; 95% CI=1.47-3.21) and preschoolers (OR= 1.76, 95% CI 1.13-2.75), respectively, in comparison to controls. No such association was seen

in adults (OR=0.90; 95% CI=0.54-1.49; Supplementary Table VI, Fig. 4).

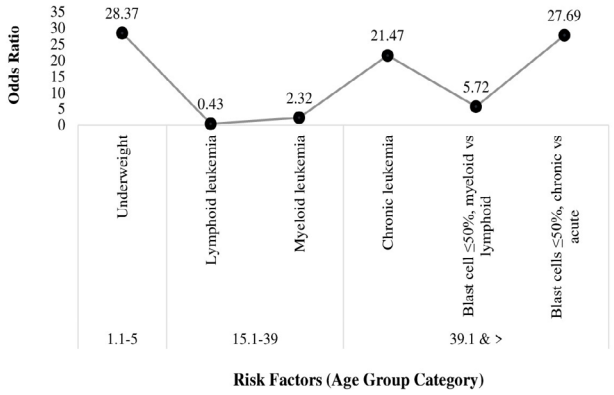

Fig. 5. Odds ratios for identification of high-risk patients age group within the patient cohort (CI 95%, p* = 0.05), showed that among patients age groups, children (1.1-5 years) with lower BMI (ref. lower BMI in remaining age groups additively) were at higher risk for the disease. Patients in age group 15.1-39 have higher tendency to get myeloid leukemia (ref. myeloid leukemia in all other age groups additively) and in patients older than 39 years of age has higher risk for chronic leukemia (ref. chronic leukemia in remaining age groups additively). In patients older than 39 years old, the blast cells % for myeloid leukemia (ref. Blast cells ≤50% in myeloid leukemia in remaining age groups additively) and chronic leukemia (ref. Blast cells ≤50% chronic leukemia in remaining age groups additively) were significantly lower than lymphoid and acute in the same age groups, respectively.

Wood use as a domestic source of fuel has a significant association with higher leukemia risk as compared to controls (OR= 3.97; 95% CI=3.14-5.01; Supplementary Table IV, Fig. 2). Particularly, children in families doing wood burning, have an elevated risk for leukemia in comparison to controls (OR= 2.01; 95% CI=1.32-3.07). No such significant association was seen in any other age group (Supplementary Table VI, Fig. 4).

The extended family setup has no overall significant risk for leukemia as compared to controls in this study; however, the preschoolers and children living in an extended family setup, have 2 (OR=2.26; 95% CI=1.43-3.58), and 3-fold increased risk (OR=3.12; 95% CI=2.05-4.77), to get the disease, respectively, when compared to the same age groups in controls. However, in adult patients, no significant increased risk was observed in comparison to adult controls (Supplementary Table VI, Fig. 4).

The consumption of carbonated drinks has been linked to an increase in leukemia risk by 25% in the present study (OR=1.25; 95% CI=1.00-1.57; Supplementary Table IV, Fig. 2).

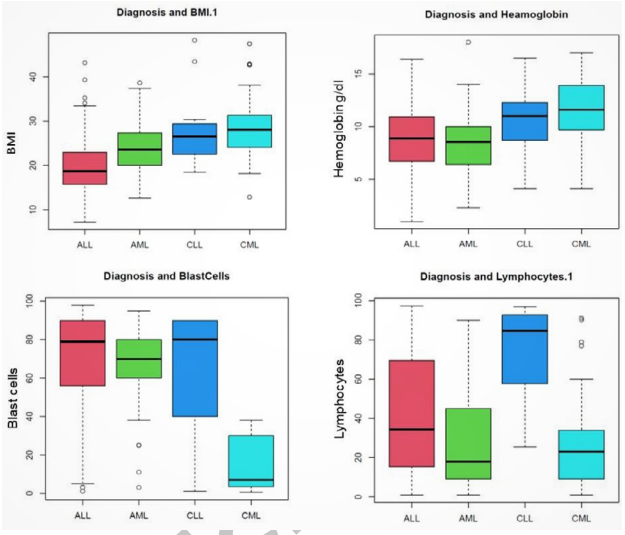

Fig. 6. Patients with acute lymphoblastic leukemia (ALL), mostly comprised of children, presents lower BMI, higher count of blast cells and lower level of hemoglobin; patients with chronic myeloid leukemia (CML), majorly comprised of adults, have been observed to have higher BMI, lower percentage of blast cells, lower levels of lymphocytes and hemoglobin. Chronic lymphoid leukemia (CLL), comprised of adults of age greater than 39 years, showed the highest count of lymphocytes unlike any other subtype.

Tobacco use (active/passive) is observed to significantly increase leukemia risk by 57% (OR=1.57; 95% CI=1.24-1.98; Fig. 2). In age group comparison, the risk was significant for the patients belonging to age group >39.1 those were using tobacco in comparison to age-matched controls (OR=2.23; 95% CI=1.37-3.62; Supplementary Table VI, Fig. 4).

Factors protecting against leukemia

In the present study, perfume use (OR= 0.42; 95% CI=0.33-0.53) and the use of microwave oven (OR= 0.25; 95% CI=0.18-0.35) were associated with a lower risk of leukemia and identified as a protective factor for the studied population (Supplementary Table IV, Fig. 2).

Hematological variables

In the current study, blast cell percentages data were obtained for patients. About 71% of the cases had >50% blast cells while 29 % had ≤50% blast cells in which most of the cases have more than 20% of blast cells (Supplementary Table III). In myeloid leukemia, age group 39.1 and > has a significant odd ratio of 5.71 for blast cell % of ≤50%, in comparison to lymphoid leukemia when compared to all other age groups (OR= 5.71; 95% CI=2.01-16.23). In chronic leukemia, blast cell ≤50% for

age group >39.1 is significantly higher than acute leukemia when compared to all other groups (OR= 27.6857; 95% CI= 7.7824-98.4913; p < 0.0001; Supplementary Table VII, Figs. 5, 6). Hyperleukocytosis (OR= 9.06; 95% CI=6.46-12.71), anemia (OR=15.84; 95% CI=11.84-21.21), lower hemoglobin level (OR= 8.11; 95% CI=6.35-10.37), thrombocytopenia (OR=32.40; 95% CI=21.57-48.68), lymphocytosis (OR=3.41; 95% CI=2.55-4.57), and neutropenia (OR=7.32; 95% CI=5.59-9.60) were the significant hematological and paraclinical risk factors associated to leukemia in the studied population (Supplementary Table V, Fig. 3).

DISCUSSION

We investigated demography, clinical aspects, and environmental and lifestyle risk factors for leukemia patients in comparison to matched controls. This study provides a measured magnitude of clinical-epidemiological risk factors associated with leukemia in the Pakistani population. The clinical and paraclinical parameters addressed in the present study were assessed to compare with the previous literature and healthy controls from the same population.

ALL was found as the most frequent leukemia subtype and Pathan ethnicity (Caucasian with debatable ancestry) was at higher risk for leukemia. Countries neighboring Pakistan also reported ALL being the highest occurring leukemia subtype, particularly in white children (Jha and Kumar, 2021). Previous literature showed that white ethnicities are more prone to leukemia compared to other ethnicities (Bispo *et al*., 2020). Differences in leukemia incidence on the base of race/ethnicity could be explained by variances in genetic susceptibility to environmental risk factors. Geographical variations play a role in leukemia distribution across the globe. It was further observed that All was common in children and adolescents while CML was frequent in adults. This finding is consistent with the data published from other countries (Hoglund *et al*., 2015; Katz *et al*., 2015).

In the present study, no education is a significant risk factor for leukemia. The observations of the present study are supported by previous literature (Mwaka *et al*., 2016; Saeed *et al*., 2019). These studies elaborate on the protective role of education in leukemia and the higher risk of leukemia with no education. No education can lead to higher incidence and lower survival of leukemia patients directly due to lack of awareness, unhealthy lifestyle, and indirectly through financial inabilities.

Poor diet and lower BMI have been identified as significant risk factors for leukemia in the present study. Poor diet is directly related to lower BMI. Studies reported the prevalence of malnutrition in children and adolescents (0-19 years of age) (Ferlay *et al*., 2015). High frequency of undernutrition and lower BMI in leukemia patients from developing countries have been associated with worse treatment outcomes, and poor survival due to lower tolerance to chemotoxicity and anti-neoplastic agents when presented at the time of diagnosis (Amankwah *et al*., 2016; Yazbeck *et al*., 2016). The mechanisms by which nutritional status might influence cancer outcomes are hypothesized to be the differential metabolic effects based on body composition (Joffe *et al*., 2019). Contrary to the current study observation, some previous cohort studies have recommended that diet is not associated with leukemogenesis (Saberi *et al*., 2014). These inconsistencies might be due to differences in study design and the population under study. The weight status of leukemia patients and its impact on risk and treatment outcome is highly debatable.

A family history of cancer (leukemia, solid cancer) and parental consanguinity are identified as significant risk factors for leukemia in this present study. Association of leukemia with consanguinity (Sandner *et al*., 2019; Mahmood *et al*., 2020) and additional features of positive family history indicate involvement of recessive cancer genes (Kakaje *et al*., 2020). Consanguinity has complicated interactions that might affect the susceptibility to certain cancers and it is known to increase the probability of having homozygosity in the genes predisposing to leukemia (Stieglitz and Loh, 2013).

In the present study, a rural residential setup, groundwater consumption, and wood usage as a source of fire are identified as significant risk factors for leukemia. Previous studies have associated these risk factors directly with leukemia and other cancers (Saeed *et al*., 2019; Kassahun *et al*., 2020; Mahmood *et al*., 2020; Jamy *et al*., 2022). Less access to supportive care in rural areas is also likely a contributing factor. In rural setups, people mostly use groundwater for drinking and burn wood as a fuel source, both of which are associated with inflammation and cancer. Pakistan is an agricultural country, exposed to heavy metals contaminated groundwater, which in turn is directly associated with increased leukemia risk (Rahmani *et al*., 2022). Heavy metals derivatives can react with side groups of proteins and enzymes, leading to genetic mutations. Contaminated groundwater with agricultural chemicals and heavy metals is a potential risk factor for leukemia in the population. In rural setups where agriculture is a major profession of the inhabitants, exposure to agrochemicals is common. The continued use of contaminated groundwater with heavy metals, insecticides, herbicides, and their naturally derived compounds for drinking and irrigation can trigger several health manifestations in the human body.

Also, the particulate and gaseous compounds produced as a result of wood combustion are linked to adverse health outcomes via systemic oxidative stress, including cancer and increased mortality due to leukemia (Avenbuan and Zelikoff, 2020). Exposure to tobacco use either directly or indirectly has also been identified in the present study as a risk factor for leukemia, like other studies (Fiebelkorn and Meredith, 2018; Frederiksen *et al*., 2020). The use of smokeless tobacco use has also been associated with cancer (Saeed *et al*., 2019).

Carbonated drinks have been observed to significantly increase leukemia risk in the present study. Likewise, a previous study reported an increased risk for childhood all due to consumption of cola-based drinks (Thomopoulos *et al*., 2015). The artificial sweeteners used in carbonated drinks have carcinogenic potential; however, there are also studies with no positive association of carbonated drinks with hematopoietic cancer (Bernardo *et al*., 2016).

Perfume and microwave oven usage has been observed as protective factors for leukemia in this study. To our knowledge, these factors have not been reported or considered in previous studies. There could be several potential justifications for these protective effects. The base/medium used in perfumery in Asian countries mostly consists of plant-based oils and fragrances are reported to have anticancer/anti-leukemic properties and the potential to induce apoptosis *in vitro* (Hung *et al*., 2020; Mileva *et al*., 2021). Along with this, perfume usage by the population is linked to general cleanliness and health consciousness, which is direct prevention. In Pakistan, the microwave oven is employed occasionally, for heating food items, instead of cooking them. This infrequent use and the fact that microwave uses weak electromagnetic waves to heat the food can potentially explain why microwave oven is not posing any risk to leukemia in the studied population; However, we do not have information regarding the frequency of microwave oven use in the study participants. The latest study claimed that the use of microwave ovens for food processing is not a risk for carcinogenesis (Guzik *et al*., 2022). However, exposure to strong electromagnetic fields (EMF) has been considered to increase the risk of leukemia (Ghahremani *et al*., 2020).

Regarding the etiology of leukemia, as this study indicated, there is the interaction of nutritional (poor diet, carbonated drinks), genetic (family history, consanguinity), and factors like poor lifestyle (lack of education, consumption of underground water, indoor burning of wood and biomass) in the development of leukemia in Pakistani population. There are changing trends in leukemia incidence due to changing demographic and lifestyle factors. Improvements in these factors hold the potential to improve the cancer burden. With the advent of proper epidemiological and trans-disciplinary research, using evidence-based local data, we can expect identification of associated risk factors and improvement in leukemia incidence and mortality.

CONCLUSION

The identification of risk factors for the Pakistani population will help the health community to address the high incidence of leukemia and design preventive strategies based on exposure to these risk factors encountered by the local population specifically and the world population in general. The limitations of the study could be small sample size in certain groups and missing data of variables.

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IRB and ethical approval

The study protocol was approved by the Ethical Review Committees of Quaid-i-Azam University (Letter No. DEBS/2016-619), Islamabad, Institute of Biomedical and Genetic Engineering (IB and GE) (Letter No. IBGE/SARK/09/1205/2012), Islamabad, and Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (Letter No. 1-1/2015/ERB/SZAMBU). The sample size was calculated by using the Daniel equation (a variant for the disease of unknown prevalence). Registered leukemia patients were enrolled from tertiary care hospitals in Islamabad and Peshawar after informed written consent of the patient/legal guardian, according to the Helsinki II declaration, from March 2017 to January 2020, and 90% of the eligible patients agreed to participate in the study.

The study was approved by the Ethics and Research Committee (details, methodology section). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent statement

Informed written consents were taken from study participants according to the Helsinki II declaration

Supplementary material

There is supplementary material associated with this article. Access the material online at: https://dx.doi.org/10.17582/journal.pjz/20221215141236

Statement of conflict of interest

The authors have declared no conflict of interest.

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Supplementary Material

Epidemiological and Clinical Correlates of Leukemia Ascertained in a Multiethnic Cohort of Pakistan

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Supplementary Table I. General characteristics of all leukemia patients (n=616) and control samples (n=884) collected from selected facilities.

Variable	Patients N (%)	Controls N (%)	Total	Variable	Patients N (%)	Controls N (%)	Total
Data present				**Family history**			
Yes	566 (91.88)	830 (93.89)	1396	Yes	34 (5.52)	12 (1.36)	46
No	50 (8.12)	54 (6.11)	104	No	582 (94.48)	872 (98.64)	1454
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
Gender				**Family type**			
Male	411 (66.72)	623 (70.48)	1034	Nuclear	109 (17.69)	162 (18.33)	271
Female	205 (33.28)	261 (29.52)	466	Extended	214 (34.74)	271 (30.66)	485
Total	616 (100)	884 (100)	1500	Unavailable	293 (47.56)	451 (51.02)	744
Blood Group				Total	616 (100)	884 (100)	1500
A	59 (9.58)	49 (5.54)	108	**Ethnicity**			
B	83 (13.47)	63 (7.13)	146	Pathan	354 (57.47)	289 (32.69)	643

Table continued on next page.....

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0030-9923/2023/0001-0001 $ 9.00/0

Variable	Patients N (%)	Controls N (%)	Total	Variable	Patients N (%)	Controls N (%)	Total
AB	30 (4.87)	18 (2.04)	48	Punjabi	191 (31.01)	494 (55.88)	685
O	54 (8.77)	54 (6.11)	108	Others	45 (7.31)	56 (6.33)	101
Unavailable	390 (63.31)	700 (79.19)	1090	Unavailable	26 (4.22)	45 (5.09)	71
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
Rh- Factor				**M. Status**			
+ve	206 (33.44)	166 (18.78)	372	Married	151 (24.51)	462 (52.26)	613
-ve	20 (3.25)	18 (2.04)	38	Unmarried	27 (4.38)	162 (18.33)	189
Unavailable	390 (63.31)	700 (79.19)	1090	Below marital Age [b]	330 (53.57)	257 (29.07)	587
Total	616 (100)	884 (100)	1500	Unavailable	108 (17.53)	3 (0.34)	111
Age Group				Total	616 (100)	884 (100)	1500
<1	7 (1.14)	10 (1.13)	17	**Education** [c]			
1.1-5	116 (18.83)	74 (8.37)	190	Educated	275 (44.64)	694 (78.51)	969
5.1-15	171 (27.76)	117 (13.24)	288	No formal education	105 (17.05)	98 (11.09)	203
15.1-39	148 (24.03)	503 (56.9)	651	Inadmissible	103 (16.72)	58 (6.56)	161
39.1 and >	152 (24.68)	180 (20.36)	332	Unavailable	133 (21.59)	34 (3.85)	167
Unavailable	22 (3.57)	0 (0)	22	Total	616 (100)	884 (100)	1500
Total	616 (100)	884 (100)	1500	Level of education			
BMI/Percentile (children)				Primary	139 (22.56)	155 (17.53)	294
Normal	128 (20.78)	210 (23.76)	338	Secondary	114 (18.51)	297 (33.60)	411
Overweight	152 (24.68)	467 (52.83)	619	Graduation	22 (3.57)	242 (27.37)	264
Underweight	123 (19.97)	152 (17.19)	275	No Formal Education	105 (17.05)	98 (11.09)	203
Unavailable	213 (34.58)	55 (6.22)	268	Inadmissible	103 (16.72)	58 (6.56)	161
				Unavailable	133 (21.59)	34 (3.85)	167
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500

Out of the total 616 patients, the data 22 were excluded in the subsequent analysis. BMI, body mass index.
[a] Weight status is derived from the BMI /Percentile (in case of children). [b] Below marital age (legal age to for marriage in Pakistan is 18 years old; Child Marriage Restraint Act, 1929 and Muslim Family Laws Ordinance, 1961). [c] Assessed by asking What is the highest grade of school completed.

Supplementary Table II. Risk factors distribution for leukemia patients (n=616) and controls (n=884).

Variable	Patients N (%)	Controls N (%)	Total	Variable	Patients N (%)	Controls N (%)	Total
Diet [a]				**Tobacco use**			
Balanced	367 (59.58)	722 (81.67)	1089	Yes	189 (30.68)	233 (26.36)	422
Poor	150 (24.35)	126 (14.25)	276	No	329 (53.41)	639 (72.29)	968
Unavailable	99 (16.07)	36 (4.07)	135	Unavailable	98 (15.91)	12 (1.36)	110
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
Microwave use				**Area** [d]			
Yes	53 (8.6)	294 (33.26)	347	Rural	265 (43.02)	252 (28.51)	517
No	406 (65.91)	573 (64.82)	979	Urban	63 (10.23)	176 (19.91)	239
Unavailable	157 (25.49)	17 (1.92)	174	Unavailable	288 (46.75)	456 (51.58)	744
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
Water Type				**Environment** [e]			
Ground water	240 (38.96)	241 (27.26)	481	Clean	124 (20.13)	302 (34.16)	426
Surface water	71 (11.53)	139 (15.72)	210	Polluted	45 (7.31)	127 (14.37)	172
Treated Water [b]	11 (1.79)	47 (5.32)	58	Unavailable	447 (72.56)	455 (51.47)	902
Unavailable	294 (47.73)	457 (51.7)	751	Total	616 (100)	884 (100)	1500
Total	616 (100)	884 (100)	1500	**Parental consanguinity**			
Fuel				CU [f]	202 (32.79)	193 (21.83)	395
Wood	287 (46.59)	206 (23.3)	493	NCU	299 (48.54)	610 (69)	909
Natural Gas	233 (37.82)	664 (75.11)	897	Unavailable	115 (18.67)	81 (9.16)	196
Unavailable	96 (15.58)	14 (1.58)	110	Total	616 (100)	884 (100)	1500
Total	616 (100)	884 (100)	1500	**Parity**			
Carbonated drinks				1	87 (14.12)	125 (14.14)	212
Yes	336 (54.55)	519 (58.71)	855	2	53 (8.6)	99 (11.2)	152
No	180 (29.22)	350 (39.59)	530	3	35 (5.68)	68 (7.69)	103
Unavailable	100 (16.23)	15 (1.7)	115	4	34 (5.52)	43 (4.86)	77
Total	616 (100)	884 (100)	1500	5	23 (3.73)	37 (4.19)	60
Perfume Use [c]				6->6	39 (6.33)	40 (4.52)	79
Yes	264 (42.86)	620 (70.14)	884	Unavailable	345 (56.01)	472 (53.39)	817
No	249 (40.42)	248 (28.05)	497	Total	616 (100)	884 (100)	1500
Unavailable	103 (16.72)	16 (1.81)	119				
Total	616 (100)	884 (100)	1500				

Out of the total 616 patients, the data 22 were excluded in the subsequent analysis, the percentages for missing data were excluded for subsequent analysis. [a]Assessed by asking Enlist the dietary item you on consume weekly basis?. [b] Treated Water; water purified by physical (filtration)or chemical techniques. [c] Perfume; Any form of liquid (perfume, body spray, attar) or powdered perfume. [d] Rural area. Villages and countryside area with diluted population and less infrastructures and services, Urban area; big town and cities with dense population and advanced infrastructure. [e] Clean environment; No noise, traffic and physical form of pollutants, Polluted environment; noise, heavy traffic, physical pollutants being encountered in routine. [f] CU, consanguineous union; NCU, non-consanguineous union.

Supplementary Table III. Hematological attributes of the leukemia patients (n=616) and controls (n=884).

Variable	Patients N (%)	Controls N (%)	Total	Variable	Patients N (%)	Controls N (%)	Total
WBC Status				**Lymphocytes (%)**			
Normal	182 (31.99)	618 (69.91)	800	Normal	135 (21.92)	544 (61.54)	679
Increment	228 (40.07)	84 (9.5)	312	Increment	152 (24.68)	96 (10.86)	248
Decrement	159 (27.94)	33 (3.73)	192	Decrement	160 (25.97)	93 (10.52)	253
Unavailable	0 (0)	149 (16.86)	196	Unavailable	169 (27.44)	151 (17.08)	320
Total	569 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
RBC Status				**Neutrophils (%) Status**			
Normal	175 (28.41)	510 (57.69)	685	Normal	119 (19.32)	533 (60.29)	652
Increment	12 (1.95)	145 (16.4)	157	Increment	33 (5.36)	57 (6.45)	90
Decrement	362 (58.77)	80 (9.05)	442	Decrement	270 (43.83)	143 (16.18)	413
Unavailable	67 (10.88)	149 (16.86)	216	Unavailable	194 (31.49)	151 (17.08)	345
Total	616 (100)	884 (100)	1500	Total	616 (100)	884 (100)	1500
Hemoglobin Status				**Blast cell ratio**			
Normal	143 (23.21)	571 (64.59)	714	≤50%	86 (13.96)		86
Increment	2 (0.32)	4 (0.45)	6	>50%	210 (34.09)		210
Decrement	425 (68.99)	161 (18.21)	586	Blank	320 (51.95)		320
Unavailable	46 (7.47)	148 (16.74)	194	Total	616 (100)		616
Total	616 (100)	884 (100)	1500	**Alkaline Phosphates**			
Platelets Status				Normal	19 (3.08)		19
Normal	185 (30.03)	645 (72.96)	830	Increment	63 (10.23)		63
Increment	58 (9.42)	62 (7.01)	120	Decrement	0 (0)		0
Decrement	323 (52.44)	29 (3.28)	352	Unavailable	534 (86.69)		534
Unavailable	50 (8.12)	148 (16.74)	198	Total	616 (100)		616
Total	616 (100)	884 (100)	1500				

Out of the total 616 patients, the data 22 were excluded in the subsequent analysis.

Supplementary Table IV. Odds ratios for demographic and life style related variables for leukemia patients in comaprison to controls.

Categories	Variables	Patients N (%)	Controls N (%)	Odds ratios	95 % CI	P values
Gender	Male	411 (66.72)	623 (70.47)	0.84	0.67-1.05	P = 0.1223
	Female	205 (33.27)	261 (29.52)	1.00		
Blood Group	B	83 (13.47)	63 (7.12)	1.11	0.74-1.68	P = 0.6011
	All others	143 (23.21)	121 (13.69)	1.00		
Rh-Factor	+ve	206 (33.44)	166 (18.77)	1.12	0.57-2.18	P = 0.7460
	-ve	20 (3.24)	18 (2.03)	1.00		
Ethnicity	Pathan	354 (57.46)	289 (32.69)	2.85	2.3-3.55	P < 0.0001
	All others	236 (38.31)	550 (62.22)	1.00		
Education	No education	208 (33.77)	156 (17.65)	3.36	2.62-4.32	P < 0.0001
	Educated	275 (44.64)	694 (78.5)	1.00		
Diet	Poor diet	150 (24.35)	126 (14.25)	2.34	1.79-3.06	P < 0.0001
	Standard diet	367 (59.57)	722 (81.67)	1.00		
Weight status	Underweight	123 (19.96)	152 (17.19)	1.96	1.49-2.58	P < 0.0001
	Normal, overweight	280 (45.45)	677 (76.58)	1.00		
Parental consanguinity	Yes	202 (32.79)	193 (21.83)	2.14	1.68-2.72	P < 0.0001
	No	299 (48.53)	610 (69)	1.00		
Family history	Yes	34 (5.51)	12 (1.35)	4.25	2.18-8.27	P < 0.0001
	No	582 (94.48)	872 (98.64)	1.00		
Area	Rural	265 (43.01)	252 (28.5)	2.94	2.1-4.11	P < 0.0001
	Urban	63 (10.22)	176 (19.9)	1.00		
Environment	Polluted	124 (20.12)	302 (34.16)	0.86	0.58-1.29	P = 0.4692
	Clean	45 (7.3)	127 (14.36)	1.00		
Water type	Ground water	240 (38.96)	241 (27.26)	2.26	1.65-3.1	P < 0.0001
	All others	82 (13.31)	186 (21.04)	1.00		
Fuel	Wood	287 (46.59)	206 (23.3)	3.97	3.15-5.01	P < 0.0001
	Gas	233 (37.82)	664 (75.11)	1.00		
Family set up	Extended	214 (34.74)	271 (30.65)	1.17	0.87-1.59	P = 0.2984
	Nuclear	109 (17.69)	162 (18.32)	1.00		
Tobacco use	Yes	189 (30.68)	233 (26.35)	1.58	1.25-1.99	P < 0.0001
	No	329 (53.4)	639 (72.28)	1.00		
Carbonated drinks	Yes	336 (54.54)	519 (58.71)	1.26	1-1.58	P = 0.0461
	No	180 (29.22)	350 (39.59)	1.00		
Microwave use	Yes	53 (8.6)	294 (33.25)	0.25	0.18-0.35	P < 0.0001
	No	406 (65.9)	573 (64.81)	1.00		
Perfume use	Yes	264 (42.85)	620 (70.13)	0.42	0.34-0.53	P < 0.0001
	No	249 (40.42)	248 (28.05)	1.00		

Supplementary Table V. Odd ratio of hematological variables for leukemia patients in comparison to controls.

Categories	Variables	Patients N (%)	Controls N (%)	Odds ratios	95 % CI	P-values
WBCs count [a]	Leukocytosis	228 (40.07)	84 (9.5)	9.07	6.47-12.71	P < 0.0001
	Normal, Leukocytopenia	341 (59.93)	651 (73.64)	1.00		
RBCs count [b]	Anemia	362 (58.76)	80 (9.04)	15.85	11.84-21.22	P < 0.0001
	Normal, Erythrocytosis	187 (30.36)	655 (74.1)	1.00		
Hemoglobin status	Lower Hb [c]	425 (68.99)	161 (18.21)	8.12	6.35-10.37	P < 0.0001
	Normal	145 (23.54)	575 (65.05)	1.00		
Platelets count	Thrombocytopenia	323 (52.43)	29 (3.28)	32.41	21.57-48.68	P < 0.0001
	Normal, Thrombocytosis	243 (39.45)	707 (79.98)	1.00		
Lymphocytes %	Lymphocytosis	152 (24.67)	96 (10.85)	3.42	2.56-4.57	P < 0.0001
	Normal, Lymphocytopenia	295 (47.89)	637 (72.06)	1.00		
Neutrophils %	Neutropenia	270 (43.83)	143 (16.17)	7.33	5.59-9.6	P < 0.0001
	Normal, Neutrocytosis	152 (24.6)	590 (66.7)	1.00		

[a] WBCs, White blood cells, [b] RBCs, Red blood cells, [c] Hb, Hemoglobin.

Supplementary Table VI. Odds ratios for high-risk leukemia patient's age groups in comaprison to control's age groups.

Variables	Risk	Risk group (Age category)	Patients N (%)	Controls N (%)	Odd ratios	95% CI	P value
Diet	Poor	1.1-5	25 (4.20)	30 (3.39)	0.70	0.38-1.26	P = 0.2326
		All other groups	115 (19.36)	96 (10.86)	1.00		
	Poor	5.1-15	59 (9.93)	27 (3.05)	2.67	1.55-4.59	P = 0.0004
		All other groups	81 (13.64)	99 (11.20)	1.00		
Parental consanguinity	Consanguineous union	1.1-5	48 (12.18)	45 (11.42)	1.03	0.65-1.64	P = 0.8951
		All other groups	153 (38.83)	148 (37.56)	1.00		
	Consanguineous union	5.1-15	80 (20.30)	57 (14.46)	1.58	1.04-2.4	P = 0.0329
		All other groups	121 (30.71)	136 (34.52)	1.00		
	Consanguineous union	39.1 and >	35 (8.88)	21 (5.32)	1.73	0.97-3.09	P = 0.0656
		All other groups	166 (42.13)	172 (43.65)	1.00		
Family history	Family history, +	5.1-15	15 (34.09)	2 (4.54)	4.41	0.83-23.42	P = 0.0814
		All other groups	17 (38.64)	10 (22.73)	1.00		
	Family history, +	5.1-15	15 (34.09)	2 (4.54)	0.48	0.02-11.37	P = 0.6473
		39.1 and >	6 (13.63)	0 (0)	1.00		
	Family history, +	39.1 and >	6 (13.63)	0 (0)	6.13	0.32-117.64	P = 0.2289
		All other groups	26 (59.09)	12 (27.27)	1.00		
Family type	Extended	5.1-15	82 (13.8)	47 (5.31)	3.13	2.05-4.77	P < 0.0001
		All other groups	121 (20.37)	224 (25.34)	1.00		
	Extended	1.1-5	56 (9.42)	39 (4.41)	2.27	1.43-3.58	P = 0.0005
		All other groups	147 (24.75)	232 (26.24)	1.00		

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Variables	Risk	Risk group (Age Category)	Patients N (%)	Controls N (%)	Odd ratios	95% CI	P value
	Extended	15.1-39	31 (5.21)	142 (16.06)	0.16	0.1-0.26	P < 0.0001
		All other groups	172 (28.96)	129 (14.59)	1.00		
	Extended	39.1 and >	33 (5.55)	36 (4.07)	1.27	0.76-2.11	P = 0.3647
		All other groups	170 (28.62)	235 (26.58)	1.00		
Area	Rural	1.1-5	66 (11.11)	39 (4.41)	1.93	1.24-3	P = 0.0036
		All other groups	187 (31.48)	213 (24.1)	1.00		
	Rural	5.1-15	103 (17.34)	51 (5.76)	2.71	1.82-4.02	P < 0.0001
		All other groups	150 (25.25)	201 (22.74)	1.00		
	Rural	15.1-39	42 (7.07)	111 (12.55)	0.25	0.17-0.38	P < 0.0001
		All other groups	211 (35.52)	141 (15.95)	1.00		
	Rural	39.1 and >	41 (6.90)	43 (4.86)	0.94	0.59-1.5	P = 0.7957
		All other groups	212 (35.69)	209 (23.64)	1.00		
Fuel	Wood	1.1-5	54 (9.09)	29 (3.28)	1.48	0.91-2.43	P = 0.1159
		All other groups	222 (37.37)	177 (20.02)	1.00		
	Wood	5.1-15	94 (15.82)	42 (4.75)	2.02	1.32-3.07	P = 0.0011
		All other groups	182 (30.64)	164 (18.55)	1.00		
	Wood	5.1-15	94 (15.82)	42 (4.75)	1.20	0.67-2.15	P = 0.5339
		1.1-5	54 (9.09)	29 (3.28)	1.00		
Water type	Ground	1.1-5	62 (10.43)	42 (4.75)	1.77	1.14-2.75	P = 0.0115
		All other groups	166 (27.95)	199 (22.51)	1.00		
	Ground	5.1-15	98 (16.49)	62 (7.01)	2.18	1.47-3.21	P = 0.0001
		All other groups	130 (21.89)	179 (20.25)	1.00		
	Ground	15.1-39	35 (5.89)	95 (10.74)	0.28	0.18-0.43	P < 0.0001
		All other groups	193 (32.49)	146 (16.52)	1.00		
	Ground	39.1 and >	33 (5.55)	38 (4.29)	0.90	0.55-1.5	P = 0.6961
		All other groups	195 (32.83)	203 (22.96)	1.00		
Tobacco use	Tobacco use	5.1-15	62 (10.43)	61 (6.90)	1.48	0.97-2.26	P = 0.0693
		All other groups	118 (19.87)	172 (19.46)	1.00		
	Tobacco use	1.1-5	34 (5.72)	33 (3.73)	1.41	0.84-2.38	P = 0.1977
		All other groups	146 (24.58)	200 (22.62)	1.00		
	Tobacco use	39.1 and >	51 (8.58)	35 (3.95)	2.24	1.38-3.63	P = 0.0011
		All other groups	129 (21.72)	198 (22.4)	1.00		
	Tobacco use	15.1-39	32 (5.38)	101 (11.42)	0.28	0.18-0.45	P < 0.0001
		All other groups	148 (24.92)	132 (14.93)	1.00		
	Tobacco use	5.1-15	62 (10.43)	61 (6.90)	0.70	0.4-1.22	P = 0.2048
		39.1 and >	51 (8.58)	35 (3.95)	1.00		
	Tobacco use	39.1 and >	51 (8.58)	35 (3.95)	1.43	0.82-2.5	P = 0.2048
		5.1-15	62 (10.43)	61 (6.90)	1.00		

Supplementary Table VII. Odds ratios for high risk patient's age groups, comparing momentous age groups with individual/combined age groups of the patients.

Categories	Variables	Risk group (Age category)	Patients (Group 1)[a] N (%)	Patients (Group 2) [b] N (%)	Odds ratios	95% CI	P value
Gender	Male	Lymphoid	278 (46.8)	122 (20.53)	1.97	1.38-2.81	P = 0.0002
		Myeloid	104 (17.5)	90 (15.15)	1.00		
	Male	Acute	298 (50.16)	102 (17.17)	1.34	0.92-1.95	P = 0.1285
		Chronic	133 (22.39)	61 (10.26)	1.00		
Diet	Poor diet, family type, extended vs nuclear	15.1-39	19 (3.19)	7 (1.17)	1.73	0.62-4.81	P = 0.2959
		5.1-15	33 (5.55)	21 (3.53)	1		
Weight status	Underweight	1.1-5	62 (10.43)	2 (0.33)	6.89	1.48-32.16	P = 0.0141
		5.1-15	54 (9.09)	12 (2.02)	1.00		
	Underweight (Normal + Overweight)	1.1-5	62 (10.43)	10 (1.68)	7.92	3.72-16.89	P < 0.0001
		5.1-15	54 (9.09)	69 (11.61)	1.00		
	Underweight (Normal + Overweight)	1.1-5	62 (10.43)	10 (1.68)	27.44	13.31-56.57	P < 0.0001
		All other groups	61 (10.27)	270 (45.45)	1.00		
	Overweight CML vs CLL	39.1 and >	53 (8.92)	13 (2.18)	0.18	0.02-1.44	P = 0.1050
		15.1-39	23 (3.87)	1 (0.16)	1.00		
	Overweight CLL vs CML	39.1 and >	13 (2.18)	53 (8.92)	5.64	0.7-45.7	P = 0.1050
		15.1-39	1 (0.16)	23 (3.87)	1.00		
Consanguinity and ethnicity	Consanguinity, Pathan vs Punjabi	5.1-15	48 (8.08)	26 (4.37)	1.45	0.78-2.66	P = 0.2368
		All other groups	60 (10.1)	47 (7.91)	1		
Fuel, water, and area	Wood, ground water, rural area vs gas	5.1-15	59 (9.93)	21 (3.53)	1.04	0.54-1.99	P = 0.9047
		All other groups	81 (13.64)	30 (5.05)	1		
	Wood, ground water, rural area vs gas	15.1-39	26 (4.37)	4 (0.67)	2.68	0.89-8.1	P = 0.0807
		All other groups	114 (19.19)	47 (7.91)	1		
	Wood, ground water, rural area vs gas	39.1 and >	24 (4.04)	4 (0.67)	2.43	0.8-7.39	P = 0.1172
		All other groups	116 (19.53)	47 (7.91)	1		
	Wood, ground water, rural area vs gas	5.1-15	59 (9.93)	21 (3.53)	0.47	0.15-1.51	P = 0.2036
		39.1 and >	24 (4.04)	4 (0.67)	1		
	Rural, ground water vs urban	5.1-15	103 (17.34)	18 (3.03)	1.02	0.35-2.99	P = 0.9686
		39.1 and >	28 (4.71)	5 (0.84)	1		
	Area rural, ground water vs urban	1.1-5	53 (8.92)	9 (1.51)	1.02	0.45-2.31	P = 0.9541
		All other groups	161 (27.1)	28 (4.71)	1		
	Area rural, ground water vs urban	5.1-15	103 (17.34)	18 (3.03)	0.98	0.49-1.97	P = 0.9536
		All other groups	111 (18.69)	19 (3.20)	1		
Area	Area, rural vs urban	1.1-5	66 (11.11)	16 (2.69)	1.28	0.65-2.52	P = 0.4713
		5.1-15	103 (17.34)	32 (5.38)	1		
Tobacco use	Tobacco use	39.1 and >	51 (8.58)	75 (12.62)	1.06	0.66 - 1.72	P = 0.7994
		5.1-15	62 (10.43)	97 (16.32)	1		
Disease origin	Lymphoid	15.1-39	73 (12.28)	75 (12.62)	0.43	0.3-0.63	P < 0.0001
		All other groups	309 (52.02)	137 (23.06)	1.00		
	Myeloid	15.1-39	75 (12.62)	73 (12.28)	2.32	1.58-3.39	P < 0.0001

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Categories	Variables	Risk group (Age category)	Patients (Group 1)[a] N (%)	Patients (Group 2) [b] N (%)	Odds ratios	95 % CI	P value
		All other groups	137 (23.06)	309 (52.02)	1.00		
Disease nature	Acute	15.1-39	103 (17.34)	45 (7.58)	0.82	0.55-1.24	P = 0.3514
		All other groups	328 (55.22)	118 (19.87)	1.00		
	Chronic	15.1-39	45 (7.58)	103 (17.34)	1.21	0.81-1.83	P = 0.3514
		All other groups	118 (19.87)	328 (55.22)	1.00		
	Chronic	39.1 and >	112 (18.85)	40 (6.73)	21.47	13.49-34.15	P < 0.0001
		All other groups	51 (8.59)	391 (65.82)	1.00		
Blast cells %	Blast cells >50%, Lymphoid vs ≤50% Lymphoid	5.1-15	76 (12.79)	21 (3.53)	1.25	0.68-2.32	P = 0.4720
		All other groups	104 (17.52)	36 (6.06)	1.00		
	Blast Cells >50%, Lymphoid vs ≤50% Lymphoid	5.1-15	76 (12.79)	21 (3.53)	1.11	0.44-2.82	P = 0.8203
		15.1-39	26 (4.37)	8 (1.34)	1.00		
	Blast Cells >50%, Lymphoid vs ≤50% Lymphoid	5.1-15	76 (12.79)	21 (3.53)	2.41	0.87-6.67	P = 0.0895
		39.1 and >	12 (2.02)	8 (1.34)	1.00		
	Blast cell ≤50% Myeloid vs ≤50%Lymphoid	39.1 and >	14 (2.35)	8 (1.34)	5.72	2.01-16.23	P = 0.0011
		All other groups	15 (2.53)	49 (8.25)	1.00		
	Blast cells ≤50%, Chronic vs Acute	39.1 and >	17 (2.86)	5 (0.84)	27.69	7.78-98.49	P < 0.0001
		All other groups	7 (1.17)	57 (9.59)	1.00		
	Blast Cells >50%, Acute VS ≤50% Acute	5.1-15	87 (14.64)	26 (4.37)	1.04	0.58-1.85	P = 0.8978
		All other groups	116 (19.53)	36 (6.06)	1.00		
	Blast Cells ≤50% Chronic vs >50%, Chronic	39.1 and >	17 (2.86)	6 (1.01)	0.18	0.01-3.61	P = 0.2619
		All other groups	7 (1.18)	0 (0)	1.00		
	Blast Cells >50%, Chronic VS ≤50% Chronic	39.1 and >	6 (1.01)	17 (2.86)	5.57	0.28-112.02	P = 0.2619
		All other groups	0 (0)	7 (1.18)			
Hemoglobin status	Hb Decrement, Blast Cells >50%, Lymphoid vs ≤50% Lymphoid	5.1-15	61 (10.26)	16 (2.69)	1.39	0.52-3.69	P = 0.5130
		15.1-39	22 (3.7)	8 (1.34)	1		
	Hb Decrement, Blast Cells >50%, Lymphoid vs ≤50% Lymphoid	5.1-15	61 (10.26)	16 (2.69)	1.91	0.57-6.37	P = 0.2946
		39.1 and >	10 (1.68)	5 (0.84)	1		
	Hb Decrement, Blast cell ≤50% Myeloid vs >50%myeloid	39.1 and >	10 (1.68)	7 (1.17)	1.63	0.4-6.63	P = 0.4927
		15.1-39	7 (1.17)	8 (1.34)	1		
Platelets status	PLT decrement, Blast cell ≤50% Lymphoid vs >50%Lymphoid	5.1-15	15 (2.52)	58 (9.76)	0.77	0.37-1.58	P = 0.4685
		All other groups	26 (4.38)	77 (12.96)	1		
	PLT decrement, Blast cell >50% Myeloid vs >50% Lymphoid	15.1-39	8 (1.34)	22 (3.70)	2.42	0.93-6.29	P = 0.0705
		All other groups	17 (2.86)	113 (19.02)	1		
	PLT Decrement, Blast cell ≤50%, Myeloid vs ≤50% Lymphoid	15.1-39	2 (0.33)	7 (1.17)	1.62	0.27-9.75	P = 0.5988
		All other groups	6 (1.06)	34 (5.72)	1		

[a] Group 1: Patients exposed to the risk variable; [b] Patients not exposed to the variable.