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FUSION GENE (TEL-AML1) OCCURRENCE IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS WITH REFERENCE TO CLINICAL AND DEMOGRAPHIC FEATURES

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Abstract:

Objective: *Children suffer from ALL (Acute Lymphoblastic Leukemia) a malignant tumour most commonly in underdeveloped countries all over the world. Various significant abbreviations of chromosomes which include translocations and also result in the fusion gene production are also in fashion (TEL-AML1, BCR-ABL and MLL-AF4). In the mentioned abbreviations fusion gene (TEL-AML1) has an association with cases of ALL. It also possesses prognostic and clinical importance. We aimed to detect fusion oncogene (TEL-AML1) frequency in the cases of ALL and its correlation to factors such as WBC, FAB subtype and age.*

Materials and Methods: *We studied 66 ALL patients at Mayo Hospital, Lahore from August 2016 to June 2017. We did not include any case of T-ALL and on chemotherapy. We analyzed data on SPSS software and assessed prognostic features such as sex, age, level of haemoglobin, platelet count, immune-phenotype, WBC profile and FAB type. We performed an RT-PCR procedure and RNA extraction in order to detect any possible fusion oncogene (TEL-AML1).*

Results: *In the total sample of sixty-six patients, fusion oncogene (TEL-AML1) frequency found in five patients (7.6%). About every case of positive (TEL-AML1) carried B-Lineage immune-phenotype, FAB ALL-L1, mean haemoglobin level (6 g/dl) and age (3 – 5) years. These parameters had a good relationship with the prognosis procedure.*

Conclusion: *Fusion gene (TEL-AML1) frequency was about 7.6% in the research subjects which is not comparable with Western studies. In case of its universal acceptance, the fusion gene (TEL-AML1) identification in cases of ALL is likely to improve the satisfaction of the risk in order to shortlist a suitable therapy.*

Keywords: *Fusion Gene (TEL-AML1), ALL (Acute Lymphoblastic Leukemia), RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction), Base Pairs (bp) and Therapeutic.*

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INTRODUCTION:

Children suffer from ALL (Acute Lymphoblastic Leukemia) malignant tumour most commonly in underdeveloped countries all over the world [1]. ALL develops because of lymphoid lineage cells maturation arrest in blood, bone marrow & related organs; another reason for its development is clonal proliferation [2]. Genetic mutations, hereditary relations and an excessive ionizing radiations exposure or chemicals exposure are also among the potential etiological agents [3]. Identification of numerous genetic alterations is available in this regard at the level of molecules [4]. In the presence of these chromosomal disorders 80% – 90% of cases are of lymphoblastic leukaemia during childhood [5].

Chromosomal disorders in ALL subjects include hyperdiploidy with under forty or above fifty chromosomes and translocation of the chromosomes e.g. t (1; 19) E2A-PBX1, t (12; 21) TEL-AML1, t (4; 11) MLL/AF4, t (9; 22) BCR-ABL1 and t (5; 14) IL3-IGH. Another important prognosis is the availability of a definitive number of chromosomal aberrations in ALL subjects. Therefore, cytogenetic disorder identification is helpful in the identification of associated ALL subtypes in the patients [6].

About 25% of the cases are of a chimeric gene (TEL-AML1) in ALL subjects [7]. Fusion transcript (TEL-AML1) positive ALL cells have an increased pro-apoptotic rote level in Fas; whereas, a decreased anti-apoptotic rote level in Bcl2 in comparison to the available negative counterparts. Positive chimeric gene (TEL-AML1) ALL cells very much sensitive to dexamethasone, vincristine and apoptotic in the presence of serum deprivation effects, which is also an important prognostic feature of ALL subtypes [8, 9]. As the age increased the molecular disorder incidence has an association with the better prognosis which includes a decrease in (TEL-AML1) and disorders linked with poor prognostic in the shape of an increase in BCR-ABL1 levels [10].

In the view of fusion gene (TEL-AML1) importance which is associated with the assessment of risk and prognosis we carried out this research to detect fusion oncogene (TEL-AML1) frequency in the cases of ALL and its correlation to factors such as WBC, FAB subtype and age

MATERIALS AND METHODS:

We studied 66 ALL patients at Mayo Hospital, Lahore from August 2016 to June 2017. We did not include any case of T-ALL and on chemotherapy. We analyzed data on SPSS software and assessed prognostic features such as sex, age, level of haemoglobin, platelet count, immune-phenotype, WBC profile and FAB type. We performed an RT-PCR procedure and RNA extraction in order to detect any possible fusion oncogene (TEL-AML1).

Peripheral vein blood sample (5 ml) or bone marrow aspirate (1 ml) sample experienced clinical assessment for CBC. We prepared smears and stained them with Giemsa for morphology; whereas, rest of the samples used in the extraction of RNA. This extraction completed in the time span of 2 – 3 hours and extracted RNA stored at a temperature of (–80 °C).

We used RT-PCR reaction for the reverse transcription of extracted RNA to cDNA with the help of specialized Kit. We synthesized cDNA through specific primers in (20 µl) volume and stored at a temperature of (–20ºC); which further helped in the amplification PCR in the availability of reverse and forward GAPDH primers. After PCR reaction, we loaded (5 – 10 µl) in two percent agarose gel. Visibility of a significant PCR product (453 bp) was then possible with the staining of ethidium bromide.

After the synthesis of cDNA, employment of (RT-PCR) us helpful for the detection of (TEL-AML1) chimeric transcript which is a result of t (12; 21) translocation. We used nested primers for RT-PCR reaction in order to attain maximum specificity and sensitivity as guided by Lin [5]. Two rounds of internal and external primers were the part of the research process. Complementary DNA helped in the performance of PCR amplification with the application of primer approach (nested RT-PCR at a rate of 35 cycles per cycle). We also completed various other procedures which include RT-reaction, PCR process and PCR amplification in the presence of necessary safety precautions and measures. Every chance of contamination experienced expert handling during the procedures. We also added positive and negative control in every amplification cycle. In the presence of 50 bp, agarose gel 2% and ethidium bromide staining; reported fusion gene (TEL-AML1) size was (181 bp).

RESULTS:

In the total sample of sixty-six patients, fusion oncogene (TEL-AML1) frequency found in five patients (7.6%). About every case of positive (TEL-AML1) carried B-Lineage immune-phenotype, FAB ALL-L1, mean haemoglobin level (6 g/dl) and age (3 – 5) years. These parameters had a good relationship with the prognosis procedure. Detailed outcomes analysis is as under:

Table – I: Demographic features (66)

Features	Groups	Number	Percentage
Age	Under 1	0	0
	1 to 10	49	74
	Above 10	17	26
Gender	Male	40	60.6
	Female	26	39.4
WBC (10^9/L)	Under 50	45	68.2
	50 - 100	12	18.2
	Above 100	9	13.6
Platelet count (10^9/L)	Under 100	57	86.4
	Above 100	9	13.6
Hemoglobin (g/dl)	Under 6	9	13.6
	6 to 9	33	50
	Above 9	24	36.4

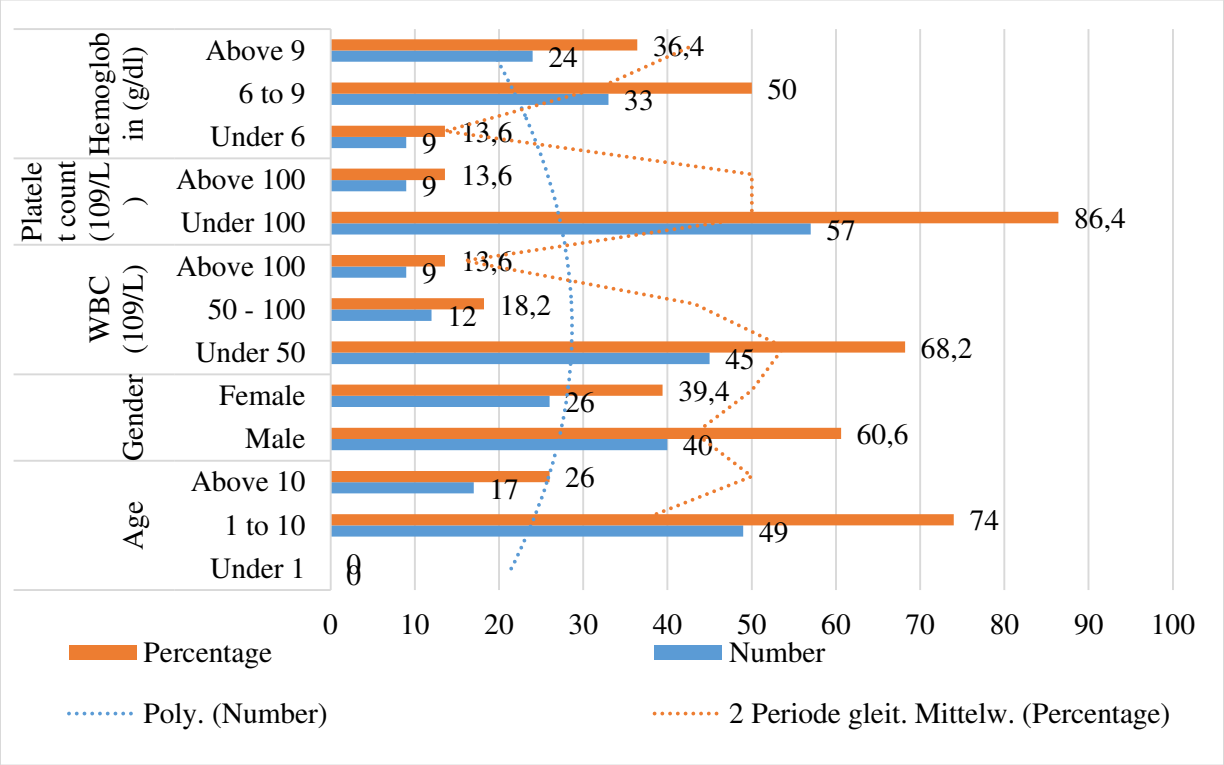


Table – II: Demographic, Clinical and Laboratory Features of positive (TEL-AML1) Cases

Sex	**Male**	**Female**	**Male**	**Male**	**Male**
Age	4	3	4	4	5
Hb g/dl	4.1	9.2	4.7	4.7	7.3
TLC 10^9/L	97.8	66.7	88.6	488.7	12.4
Platelet count 10^9/L	193	13	61	29	90
Lymphadenopathy	Present	Absent	Absent	Absent	Present
Hepatomegaly	Present	Present	Present	Present	Present
Splenomegaly	Present	Present	Present	Present	Present
FAB type	L1	L1	L1	L1	L1
Immune-phenotype	Pre-B	Pre-B	Pre-B	Pre-B	Pre-B

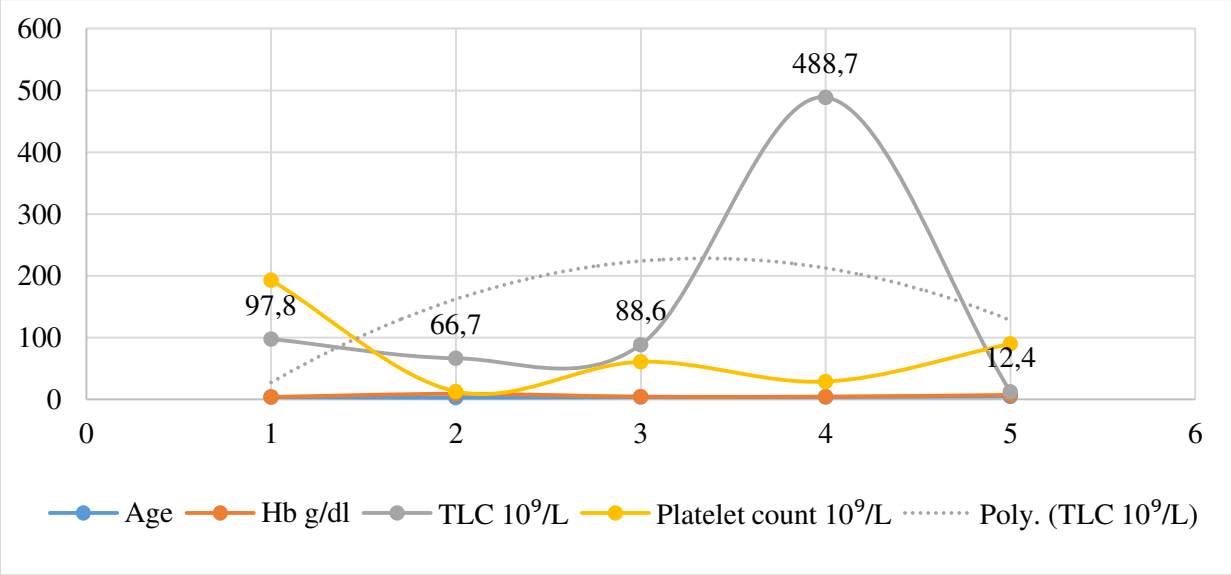
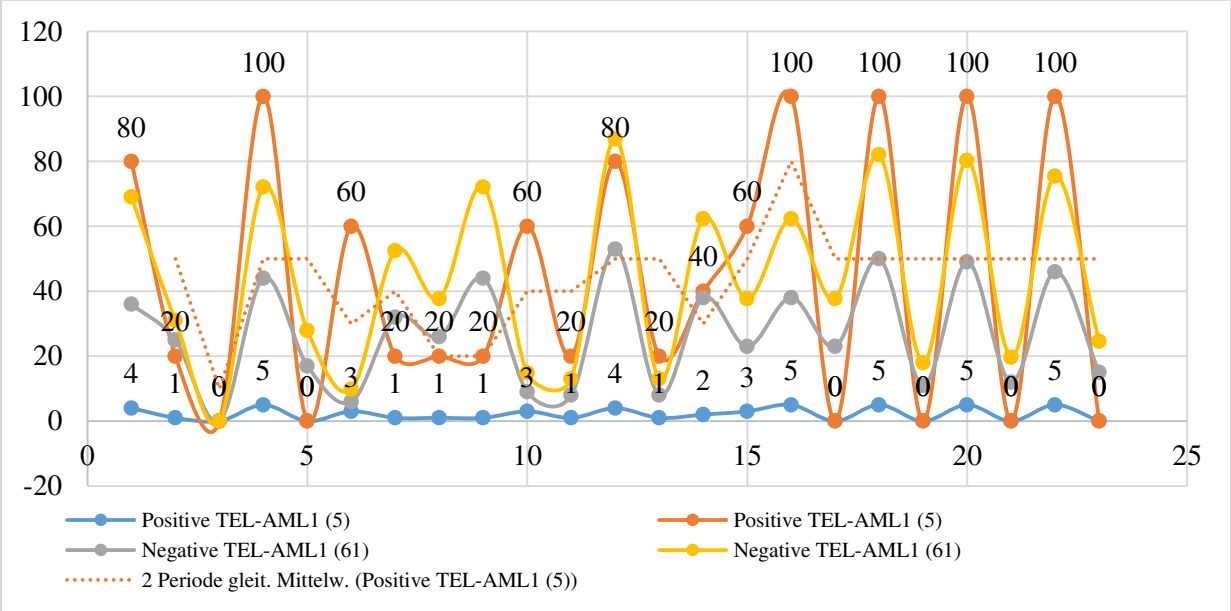


Table – III: Laboratory and Clinical Features of Negative & Positive (TEL-AML1) Patients

Features / Parameters		Positive TEL-AML1 (5)		Negative TEL-AML1 (61)	
		Number	Percentage	Number	Percentage
Gender	Male	4	80	36	69
	Female	1	20	25	31
Age (Years)	< 1	0	0	0	0
	1 to 10	5	100	44	72.1
	> 10	0	0	17	27.9
Hemoglobin	< 6	3	60	6	9.8
	6 to 9	1	20	32	52.5
	> 9	1	20	26	37.7
TLC ($x10^9$/L)	< 50	1	20	44	72.1
	50 to 100	3	60	9	14.8
	> 100	1	20	8	13.1
Platelet count ($x10^9$/L)	< 100	4	80	53	86.9
	> 100	1	20	8	13.1
Lymphadenopathy	Present	2	40	38	62.3
	Absent	3	60	23	37.7
Hepatomegaly	Present	5	100	38	62.3
	Absent	0	0	23	37.7
Splenomegaly	Present	5	100	50	82
	Absent	0	0	11	18
FAB Type	ALL-L1	5	100	49	80.3
	ALL-L2	0	0	12	19.7
Immune phenotypes	Pre-B	5	100	46	75.4
	Precursor-B	0	0	15	24.6



DISCUSSION:

Genetic aberrations translocations are about 75% in ALL cases. Their detection is necessary in order to avoid possible treatment risks [11]. Fusion Gene (TEL-AML1) is a common genetic aberration reported ALL cases (B-lineage) in the West [12]. Sensitivity to chemotherapy in TEL-AML-1 is also evident in the positive ALL cells which indicates a better ALL subtypes prognostic [8]. Racial variations are because of the geographic variations that cause the variation in the fusion gene between various countries of South-East Asia especially a country like Pakistan. We aimed to detect fusion oncogene (TEL-AML1) frequency in the cases of ALL and its correlation to factors such as WBC, FAB subtype and age.

Females were dominating males in the positive cases of (TEL-AML1) with a proportion of four to one patients; Hebam Shaker is of the same view [13]. Peak incidence targeted an age bracket of 2 – 5 years in children [14]. We reported 48 patients (73%) in the age of under ten-years same observation is also available in another study [9]. Mean age factor was (10.76 ± 12.86) years. Most important information was in the age leukocyte count and age of the patient during diagnosis [13]. On the basis of age distribution and clinical outcomes, the positive (TEL-AML1) cases fall in the risk group [9, 13].

Hepato-splenomegaly is most common outcomes present in these patients. Forty-three cases belonged to Hepatomegaly (65.2%); whereas, 55 cases belonged to splenomegaly (83.3%). Other studies are comparable with our research outcomes about organomegaly [6, 11]. Only one case were of lymphadenopathy in the five cases of positive (TEL-AML1); whereas, splenomegaly and hepatomegaly were present the all positive cases of positive (TEL-AML1). This is also the same as reported in various other research studies [6]. Outcomes of WBC, Hemoglobin (Hb) and Fab type are also comparable with various other authors such as Pandita and others [5, 6, 9, 11].

As we observed that five cases were of positive fusion gene (TEL-AML1) (7.6 %); which is the same as observed in the local and international research studies [6, 15]. Local and international studies had respective (TEL-AML1) fusion gene frequency of 9.7% & 8.69%. USA and Taiwan researchers reported different outcomes which do not match our research outcomes as the higher frequencies are present in these research studies about positive (TEL-AML1) with respective proportions of 26% & 32%. Spanish author also reported a fusion gene (TEL-AML1) frequency as 0.00% in his research [16].

These variations in the fusion gene (TEL-AML1) are due to various environmental and genetic factors which contribute to ALL pathogenesis. Our outcomes are very close to the reported outcomes at international and national level. Similarities are possible common as lifestyle, environment and diet intake is almost the same.

CONCLUSION:

ALL cases reported a fusion gene (TEL-AML1) frequency of 7.6% in this research study. Better prognosis features are available in the age of 3 – 5

years. Distinct clinical entities include B-Lineage immune-phenotype, FAB type, level of mean haemoglobin (6 g/dl) and ALL-L1 in the positive (TEL-AML1) patients. Fusion gene (TEL-AML1) frequency was about 7.6% in the research subjects which is not comparable with Western studies. In case of its universal acceptance, the fusion gene (TEL-AML1) identification in cases of ALL is likely to improve the satisfaction of the risk in order to shortlist a suitable therapy.

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