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IGH gene rearrangement in Acute Lymphoid Leukemia: A study from western region of India

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***Abstract*—**Acute lymphoblastic Leukemia (ALL) is found to be a heterogeneous disorder that coexists with multiple clones. The treatment and outcome of ALL is dependent on risk stratifications of ALL patients that is decided on the basis of prognostic factors such as WBC count, age, immunophenotype and cytogenetic aberrations. There are about 75% of ALL patients that harbors recurring chromosomal aberrations out of which 5% had IGH gene rearrangement. This rearrangement can be detected by Fluorescence *in situ* Hybridization (FISH). The present work was conducted for studying the prevalence of IGH gene rearrangement and to correlate it with prognostic factors and survival. In the present study, blood, and bone marrow of newly diagnosed 50 ALL patients were included. Molecular cytogenetic method i.e., FISH was used to identify rearrangement in IGH gene present on chromosome 14q32 using IGH break apart probe. The results were statistically analyzed using SPSS software and were considered statistically significant when p value ≤ 0.05. In the present study, 14 (28%) patients had signal pattern other than 2F. Among 14 patients with abnormal signal pattern, 9 (18%) had rearrangement of IGH gene (OGF), 4 (8%) had gain of IGH gene (FFF/FFFF) and 1 (2%) had loss of IGH gene (F). IGH gene rearrangement and IGH gene abnormality (IGH gene rearrangement, IGH gene gain and IGH gene loss) was found to be significantly associated with B-ALL subtype. Also, IGH gene abnormality was significantly correlated with patients belonging to younger age group and absence of splenomegaly. Additionally, out of total 9 patients with IGH gene rearrangement, 3 (33%) patients died and all of them were of B-ALL subtype. FISH is a powerful tool to analyze cytogenetic abnormalities in patients with ALL. IGH gene rearrangement defines a genetic feature that is frequent among patients with Acute Lymphoblastic Leukemia. Moreover, patients with IGH gene rearrangement and of B-ALL subtype showed poor prognosis.

Keywords*—ALL, IGH gene, Fluorescence in-situ hybridization*

I. INTRODUCTION

Leukemia seems to be associated with genetic changes or chromosomal abnormalities, especially Acute Lymphoblastic Leukemia (ALL) which is found to be differentiated by translocations and chromosomal rearrangement. The various genetic aberrations observed in ALL patients are important indicators of prognosis, which are now extensively used for risk stratification [1]. Immunoglobulin heavy chain locus (*IGH@*) is found to be frequently translocated which is considered as hallmark of mature B-cell malignancies. This sporadically causes malignant transformation of cells and drive pathogenesis [2, 3]. This phenomenon of translocation of protooncogenes in IGH locus is termed as IGH rearrangement which is one of the most common findings in mature B cell tumours [4]. It results in juxtaposition of IGH gene enhancer, due to which the nearby otherwise silent oncogene is activated and overexpressed [5]. Commonly involved oncogenes are transcription factors and cytokine receptor gene.

IGH gene rearrangement is found to be linked with other abnormalities such as Hyperdiploidy, DUX4 overexpression, BCR-ABL positivity and MLL gene rearrangements [6]. IGH gene rearrangement can be present as primary or secondary event and is found to be linked with higher NCI risk group patients. Also, patients with IGH translocations are known to have increased relapse rate and poor survival. The genes juxtaposition and deregulated may play vital roles in hematopoietic development and thus have unfavourable outcomes on cell function [5]. Based on this, the present study aimed to identify IGH gene rearrangement in patients with ALL and further correlate the observed results with various clinicopathological variables and survival outcome of the enrolled patients.

II. MATERIALS & METHOD

Subjects

The present study enrolled 50 de novo ALL patients diagnosed at The Gujarat Cancer & Research Institute (GCRI). The diagnosis of all the cases was done based on morphology, cytochemistry and flow cytometric analysis

by the pathologists of the institute. Institutional Scientific Review Board and Ethics Committee approved the study. General consent was taken in prior from all the patients.

Fluorescence *in situ* Hybridization (FISH)

Bone marrow (BM) aspirate as well as blood samples were collected and direct harvesting of cells using hypotonic solution was carried out. This was followed by the fixation using acetic acid/methanol (1:3) and the cell suspension was used to prepare the slides. IGH plus Break Apart Rearrangement Probe procured commercially was used for studying the rearrangements in IGH gene. Co-denaturation of target DNA and probe DNA was carried out for 2 minutes at 75^0 C and then hybridization at 37^0 C overnight. Post-hybridization washes were carried out next day in 0.4X SSC/ 0.3% NP-40 for 2 minutes at 73^0 C and then in 2X SSC/ 0.1% NP-40 for 1 minute at room temperature and allowed to air dry in the dark followed by counterstaining with DAPI. The slides scanning and capturing was done using Epifluorescence microscope (Zeiss) at a magnification of 63X. The probe when hybridized to a normal nucleus gave a two orange/green (yellow) fusion (2F) signal pattern, while when the nucleus was presented with IGH translocation, the probe gave one orange, one green, and one orange/green fusion signal pattern (1O1G1F).

Statistical analysis

The data obtained from the experiment was evaluated statistically using SPSS Inc. version 16 software. Correlation between IGH gene aberrations and various categorical data was done by two-tailed chi square test and spearman's correlation method. Survival analysis of the enrolled patients was done using Kaplan-Meier method and Log rank test was used to assess the prognostic significance of OS. The results were considered statistically significant when $P \leq 0.05$.

III. RESULTS

Clinicopathological characteristics of ALL patients

The study included total 50 ALL patients, of which 32 (64%) were males and 18 (36%) were females and the median age was 14 years. The youngest enrolled patient was 1 year and the oldest one was of 71 years. Based on median age, patients were divided into subgroups consisting those with younger age (<14 years) and older age (≥ 14 years). Of total enrolled patients, 10 (20%) patients were known cases of T-ALL and 40 (80%) patients were of B-ALL. Amongst 40 (80%) patients with B-ALL, 26 (52%) patients had mature B-ALL, 13 (26%) had pre-B-ALL and 1 (2%) had early pre-B-ALL. Out of 10 (20%) patients with T-ALL, 7 (14%) had mature T-ALL, 2 (4%) had pre-T-ALL and 1 (2%) had early pre-T-ALL. Table 1 enlists the clinicopathological features of the enrolled patients.

Table 1: Demographics and clinical characteristics of ALL patients

Characteristics	N (%)
Total	50(100%)
Age (Range: 1-71 years)	
Median: 14 years	
< 14 years	26 (52%)
≥ 14 years	24 (48%)
Sex:	
Male	32 (64%)
Female	18 (36%)
Haemoglobin(Range: 3.9-12.9 g/dl)	
Median: 7.7 g/dl	
<7.7 g/dl	26 (52%)
≥ 7.7 g/dl	24 (48%)
Erythrocytes (Range: 1.510-4.770 x 10^6cells/µL)	
Median: 2.615 X 10^6 µL	25 (50%)
< 2.615 X 10^6 µL	25 (50%)
≥ 2.615 X 10^6 µL	
WBC (Range: 0.360-772.390 x 10^3cells/µL)	
Median: 17.485 x 10^3cells/µL	
< 17.485 x 10^3cells/µL	25 (50%)
≥ 17.485 x 10^3cells/µL	25 (50%)
Platelets (Range: 3.0-169.0 x 10^3cells/µL)	
Median: 28.5 x 10^3cells/µL	
< 28.5 x 10^3cells/µL	25 (50%)
≥ 28.5 x 10^3cells/µL	25 (50%)
Blasts (Range: 7 – 97 %)	
Median: 74.50%	
< 74.50%	25 (50%)
≥ 74.50%	25 (50%)
Philadelphia	
Negative	39 (78%)
Positive	11 (22%)
Splenomegaly	
Absent	20 (40%)
Present	29 (60%)
ALL subtype:	
B-ALL	40 (80%)
Ph negative	30 (75%)
Ph positive	10 (25%)
T-ALL	10 (20%)

Additional Cytogenetic Abnormalities

Of the total 50 patients included in the study, 19 (38%) patients had normal karyotype, 16 (32%) patients had various cytogenetic changes while there were no metaphases observed in 15 (30%) patients due to low proliferative index. Out of 16 patients with cytogenetic changes, 6 (12%) patients had only BCR-ABL translocations and remaining 10 (20%) patients had additional cytogenetic changes [Table 2].

Table 2: Patients with additional cytogenetic abnormalities

Patient no.	**Age**	**Sex**	**Diagnosis**	**Karyotyping**
12	9	M	PRE-B-ALL	2n+[5]/46,XY[4]
17	15	M	B-ALL	47,XY,+der22t(9;22)(q34;q11.2), t(9;22)(q34;q11.2) [3]/ 46,XY, t(9;22)(q34;q11.2)[4]/ 46,XY[2]
26	22	F	PRE-B-ALL	46,XX,t(7;12)(q?36;p?13), t(9,22)(q34;q11.2)[20]
27	2	M	B-ALL	46,XY,t(12;21)(p13;q22)[8]/ 46,XY [3]
36	27	F	B-ALL	COMPLEX CHROMOSOMAL REARRANGEMENTS[15]/ 46XX[5]
39	14	M	PRE-T-ALL	46, XY, t(1;7) (p32;q36) [4]/ 46,XY[1]
41	7	F	T-ALL	46,XX del(11) (q23) [3]
46	18	F	B-ALL	2n + [6]
48	16	F	PRE-B-ALL	46,XX,t(4;11)(q21;q23)[20]
50	8	M	PRE-B-ALL	2n+ [20]

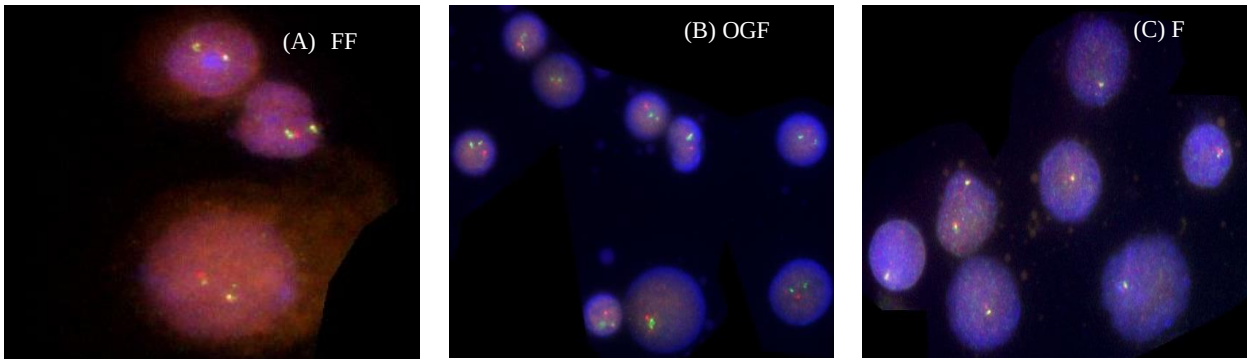
Among the 10 patients with additional cytogenetic abnormalities, 3 patients (no. = 12, 46 and 50) had Hyperdiploidy. Patient no. 17 had derivative chromosome 22 along with BCR-ABL translocation. Patient no. 26 showed translocation of genes between chromosome 7 and 12 [t(7;12)(q?36;p?13)] along with BCR-ABL translocation. Patient no. 27 had translocation of chromosome 12 and 21 [t(12;21)(p13;q22)] and patient no. 36 had complex chromosomal rearrangement. Patient no. 39 showed translocation between chromosome 1 and 7 [t(1;7)(p32;q36)] and patient no. 41 had deletion of chromosome 11. Patient no. 48 showed translocation of genes involving the chromosome 4 and 11 [t(4;11)(q21;q23)].

IGH gene incidence

Out of total enrolled ALL patients in the study, 9 (18%) were detected with rearrangement of IGH gene. All these patients with IGH gene rearrangement belonged to B-ALL. Along with IGH gene rearrangement, gain of IGH gene locus and deletion of IGH gene locus was also detected. Among 9 patients with IGH rearrangement, 4 patients displayed typical IGH rearrangement patterns (OGF). One of these patients exhibited gain of IGH gene locus (FFF / FFFF), possibly signifying trisomy 14, one patient showed IGH gene rearrangement with gain of IGH gene (OGFF), one patient revealed a IGH 5' variable region sub-microscopic deletion along with IGH gene rearrangement (OF), one patient had IGH gene rearrangement with loss of normal haplotype (OG) and one patient had IGH gene rearrangement with gain of IGH gene (OGFFF). Based on different IGH signalling patterns, patients were divided into different subgroups as shown in Table 3. FISH result images of the obtained signal patterns are shown in Figure 1.

Table 3: IGH gene incidence

IGH gene Incidence	
Rearrangement	**N (%)**
No rearrangement	41 (82%)
Rearrangement	9 (18%)
Gene signal pattern	**N (%)**
Normal 2F	36 (72%)
Other than 2F	14 (28%)
Gene status	**N (%)**
Normal result	36 (72%)
IGH gene rearrangement	9 (18%)
Gain of IGH gene locus	4 (8%)
Loss of IGH gene locus	1 (2%)



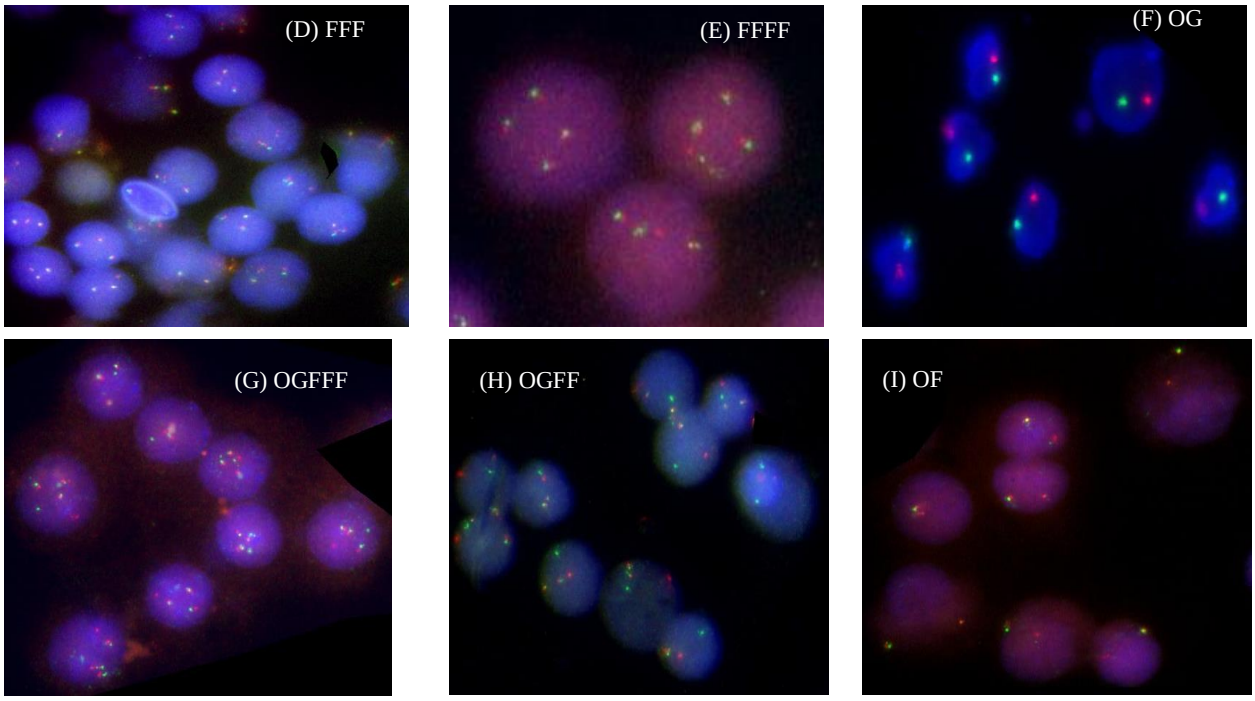


Figure 1: Signal pattern observed for IGH break-apart probe
(A) FF: No rearrangement, (B) OGF: IGH gene rearrangement, (C) F: Loss of IGH gene, (D) FFF and (E) FFFF: Gain of IGH gene (F) OG: IGH gene rearrangement with loss of normal haplotype, (G) OGFFF and (H) OGFF: IGH gene rearrangement with gain of IGH gene locus, (I) OF: One normal IGH locus with sub-microscopic deletion of IGH 5' variable region

Demographics and clinical characterization of patients divided in different subgroups:
As shown in Table 4, IGH gene rearrangement status was correlated with the demographics and clinical characterization of the enrolled patients with ALL. A significant high incidence of IGH gene rearrangement was observed in patients with B-ALL as compared to patients with T-ALL ($p = 0.03$). No other significant associations were observed with rest of the parameters. The patients were divided based on normal and abnormal pattern observed in IGH gene and correlation was done with the demographics and clinical characteristics of the patients. IGH gene abnormality was significantly associated with patients in younger age group ($p = 0.02$), patients with B-ALL ($p< 0.01$) and patients without splenomegaly ($p = 0.01$) when compared to their respective counterparts. Also, high incidence of IGH gene abnormality was observed to have trend in patients with low WBC count as compared to patients with high WBC count ($p = 0.06$). No other significant correlations were observed for rest of the parameters.

Table 4: Demographics and clinical characterization of patients in different subgroups

Characteristics	**Total patients N (%)**	**Negative N (%)**	**Positive N (%)**	χ^2	**R value**	**p value**
IGH gene rearrangement						
Total	50 (100%)	41 (82%)	9 (18%)			
Immunophenotype						
T-cell	10 (100%)	10 (100%)	0 (0%)	2.74	0.23	**0.03**
B-cell	40 (100%)	31 (77%)	9 (23%)			
Abnormal IGH gene						
Age						
Younger (<14)	26 (100%)	15 (58%)	11 (42%)	5.50	-0.33	**0.02**
Older (≥14)	24 (100%)	21 (87%)	3 (3%)			
Immunophenotype						
T-cell	10 (100%)	10 (100%)	0 (0%)	4.86	0.31	**<0.01**
B-cell	40 (100%)	26 (65%)	14 (35%)			
WBC x 10^3 cells/µL						
< 17.485	25 (100%)	15 (60%)	10 (40%)	3.57	-0.27	0.06
≥ 17.485	25 (100%)	21 (84%)	4 (16%)			

Demographics and clinical characterization of patients with IGH gene cytogenetic aberrations

Based on different IGH gene cytogenetic aberrations, patients were divided into different subgroups and correlation was done with the demographics and clinical characteristics of the patients [Table 5]. A significant association was found between younger age patients and absence of IGH gene rearrangement (58%), followed by presence of IGH gene rearrangement (23%), gain of IGH gene (15%) and loss of IGH gene (4%) (p = 0.03) as compared to older patients. A significant correlation was observed between patients with B-ALL subtype and absence of IGH gene rearrangement (65%), followed by IGH gene rearrangement (22%), gain of IGH (10%) and loss of IGH gene locus (3%) (p= 0.05). A high incidence of no IGH gene rearrangement in patients without splenomegaly was observed to have trend (55%), followed by IGH gene rearrangement (25%), gain of IGH (15%) and loss of IGH (5%) (p = 0.07).

Table 5: Correlation between ALL patients' characteristics and IGH gene aberrations.

Demographics or clinical characteristics	Total patients N (%)	No rearrangement N (%)	Rearrangement N (%)	Gain of IGH N (%)	Loss of IGH N (%)	χ^2	R value	p value
Total	50 (100%)	36 (72%)	9 (18%)	4 (2%)	1 (2%)			
Age								
Younger (<14)	26 (100%)	15 (58%)	6 (23%)	4 (15%)	1 (4%)	6.93	-0.37	**0.03**
Older (≥14)	24 (100%)	21 (87%)	3 (13%)	0 (0%)	0 (0%)			
IPT								
T-cell	10 (100%)	10 (100%)	0(0%)	0(0%)	0(0%)	4.86	0.28	**0.05**
B-cell	40 (100%)	26 (65%)	9 (22%)	4 (10%)	1 (3%)			
Splenomegaly								
No	20 (100%)	11 (55%)	5 (25%)	3 (15%)	1 (5%)	6.51	-0.36	0.07
Yes	29 (100%)	25 (86%)	3 (10%)	1 (4%)	0(0%)			

Survival outcome

Amongst the ALL patients observed with IGH gene rearrangement (n=9), three (33%) died within 25 days of diagnosis. Thirteen (32%) out of 41 (100%) patients without rearrangement died. In total ALL patients, survival analysis indicated no significant correlation with the survival outcome between patients having IGH rearrangement and those not having IGH rearrangement.

IV. DISCUSSION

ALL is The most frequent cancer being diagnosed in children is ALL that represent 60% of cancer cases among children and younger adults less than 20 years [SEER-2018]. In spite of improvement in diagnosis, ALL still have poor prognosis in developing countries. Genetic aberrations are important factors to determine the prognosis in ALL and are extensively used for risk stratification [1]. Various factors play role in treatment decision making but genomic data is of preeminent [7]. One such important cytogenetic aberration is rearrangement of IGH gene. It is an independent prognostic factor for duration of OS and DFS [Russell et al, 2014] [5]. Thus, in order to improve the survival of patients in ALL, it is important to conduct research for IGH gene rearrangement status in these patients.

The present study enrolled ALL patients with age ranging from 1 to 71 years having mean and median age of 14.56 and 14 years, respectively having majority of study population below 18 years. Similarly, Yilmaz et al. reported 15 years of median age in ALL patients in their study [8]. Out of 50 patients, 64% patients were male, which is consistent with the results reported by Kakaje et al. showing male predominance with 60.9% patients [9]. The same study also reported 20.2% occurrence of T-ALL. This data is similar to our study in which T-ALL was found in 20% of study cohort. In the present study, haemoglobin levels of the patients ranged from 4.1 - 12.9 g/dl with median of 7.7 g/dl. Similar results with median haemoglobin of 7.5g/dl was reported by Jaime et al. in their study [10]. They also reported 82.9% cases with anaemia at the time of diagnosis. However, present study had 98% ALL patients with anaemia. The median leukocyte count of ALL patients in present study was 17.485 x 10^3 cells/µL with a range of 0.360 – 772.390 x 10^3 cells/µL. However, Xing et al. observed a median leukocyte count of 11.50 x 10^3 cells/µL in their patients [11]. The difference in the value can be attributed to the study cohort selected by Xing et al. which consisted of patients with age ≥ 14 years. Additionally, in the present study, anaemia and hepatosplenomegaly were predominant clinical manifestations at presentation. Laboratory findings also showed high level of leukemic cells which resulted in patients having high WBC count, low haemoglobin level and low platelet count. These results were concurrent with study done by Lustosa et al. and Saeedi et al. [12, 13]. They observed hepatosplenomegaly to be the most frequent clinical features in ALL patients and patients with high WBC count had inferior outcomes.

Further, in the present study, 6% patients had hyperdiploidy, similar incidence of hyperdiploidy is reported by Chen et al. [14]. A single patient in present

study had derivative chromosome 22 along with BCR-ABL translocation, in accordance with Short et al. showing inferior outcomes of patients with this aberration [15]. Also, a patient had translocation of genes between chromosome 7 and 12 [t(7;12)] along with BCR-ABL translocation which is consistent with Von et al. [16]. Translocation involving chromosome 12 and 21 [t(12;21)] was also observed in this study and similar results were also reported by Shago [17]. A patient in this study showed complex chromosomal rearrangement. Motlló et al. also observed presence of complex chromosomal rearrangement in ALL patients and showed unfavourable outcome for these patients [18]. A patient in this study had translocation between chromosome 1 and 7 [t(1;7)] which is in accordance with Russell et al. [5]. Deletion of chromosome 11 is also observed in the present study which is consistent with Pui et al. findings [19]. A patient in present study showed translocation of genes between chromosome 4 and 11 [t(4;11)], in accordance with Hutspardol et al. [20].

IGH gene present on chromosome 14 might be involved in various types of translocations such as t(9;14) (p11-12,q32.3) and t(14;14) (q11.2,q32.3) which might lead to deletion or activation of partner gene. Various signal patterns for IGH break-apart probe is observed in the present study. Abnormal signal patterns like OG for IGH gene rearrangement with loss of normal haplotype, OGYYY for IGH gene rearrangement with gain of IGH locus and OY for IGH gene rearrangement with sub-microscopic loss of 5' variable region was found in our study. IGH gene rearrangement in ALL patients of present study was found to be 18%. Similarly, 14% incidence of IGH gene rearrangement in multiple myeloma patients and 13% in CLL patients has been reported by Huh et al [21]. This indicates characteristic abnormality of the IGH gene rearrangement in other malignancies too. However, in ALL patients the prevalence of IGH gene rearrangement is quite low than the present study. Russell et al. reported 5% incidence of IGH gene rearrangement in BCP-ALL and T-ALL [5]. At the same time they observed IGH gene rearrangement in 16% DS-ALL which is similar to our data. Further, several other studies reported IGH rearrangement in 6.3% (Hutspardol et al., 2012) [20], 5% (Shago 2017) [17], 9.5% of ALL patients [22], <5% childhood and 10 % of adults ALL patients [23].

Furthermore, the present study has observed ALL patients with gain as well as loss of IGH gene. Similar results are being reported previously with 21.9% patients showing an extra copy of gene [20]. In the present study, 8% ALL patients were found to have an extra copy of IGH while there was a single patient having deletion of IGH gene locus. Consistently, Huh et al. also showed a single ALL case which had a deletion of IGH gene locus [21]. In addition, correlation of IGH gene rearrangement with various clinico-pathological features found its association with B-ALL. Also, patients with IGH gene abnormality had significantly lower WBC count (< 17.485 x 10^3 cells/µL). Our findings were in discordance with those reported by Russell et al. [5]. They found no association of IGH gene status with respect to sex and WBC. Also, according to their study IGH gene rearrangement incidence was more frequent in older age group. Similar findings were reported by Shago showing high incidence of IGH gene rearrangement in adolescents and young adults [17]. There was no significant association between IGH gene rearrangement and survival outcome in present study. However, Russell et al. showed poor event-free survival and overall survival for patients with IGH gene rearrangement [5].

V. CONCLUSION

The incidence and spectrum of IGH gene translocations in ALL raises the question of its importance in development of leukemia. It might be possible that the genes associated with these translocations may play vital role in hematopoietic development. Thus, genes deregulated because of IGH translocations can have diverse effect depending on the biologic function of the cell type. It leads to a logical assumption that clinical relevance and outcome of IGH gene translocations depends on the function of the partner gene. Further study on partner genes may open a new window for treatment for ALL patients with IGH gene rearrangement.

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Conflict of interest
None

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