



Challenges in Care of Children with Acute Leukemia in a Government Hospital in India: A Retrospective Analysis

Ankita Sen¹ Prantar Chakrabarti² Shuvra N. Baul¹ Asoke K. Talukder³ Prakas K. Mandal¹
Rajib De¹ Shyamali Dutta¹ Tuphan K. Dolai¹

¹Department of Haematology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India

²Department of Haematology, Vivekananda Institute of Medical Sciences, Kolkata, West Bengal, India

³SRIT, Bengaluru, Karnataka, India

Address for correspondence Ankita Sen, MD, DM, Department of Haematology, Nil Ratan Sircar Medical College & Hospital, 138, Acharya Jagadish Chandra Bose Road, Kolkata 700014, West Bengal, India (e-mail: drankitasen2019@gmail.com).

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Abstract

Introduction Acute leukemia (AL) is among the most common treatable cancers in childhood but many children are forced to abandon therapy.

Objective We have explored reasons for treatment abandonment through this study.

Materials and Methods Retrospective analysis from an ongoing registry data of childhood AL patients, where all newly diagnosed AL patients of ≤ 18 years of age (June 2014–November 2017) were included. Patients >18 years of age, having any history of treatment of AL outside our institute, and/or patients with relapsed AL were excluded. The primary outcome of the study was treatment abandonment rate.

Results A total of 710 AL patients were included in the study, average distance traversed to reach the hospital being 161.66 km. Most children were aged 1 to 10 years (49.4%, $n = 351$), followed by >10 to 18 years (46.6%, $n = 331$), and ≤ 1 year age (3.9%, $n = 28$). The commonest symptoms were fever (67.4%), pallor (38.6%), bleeding (11.5%), bone pain (13.8%), neck swellings (14.9%), and, rarely, testicular swellings or Superior vena cava (SVC) syndrome (1.1%). A high abandonment rate was noted prior to leukemia subtyping (35.2%, $n = 250$) mostly among males 62% ($n = 155$) and the 1- to 10-year group 55.6% ($n = 139$). A total of 460 (64.8%) patients were subsequently subcategorized by immunophenotyping. Precursor B-cell (Pre-B) Acute Lymphoblastic Leukemia (ALL) in 307 (43.2%) patients was the commonest subtype, followed by early Pre-B ALL (Pro-B ALL) in 10 (1.4%), T-cell ALL (T-ALL) in 51 (7.1%), Acute Myeloid Leukemia (AML) in 45 (6.3%), Acute Promyelocytic Leukemia (APML) in 28 (3.9%), and Mixed Phenotypic Acute Leukemia (MPAL) in 19 (2.6%).

Conclusion The most common group of patients was aged 1 to 10 years (median age: 5 years). An abandonment rate of 35.2% was seen prior to complete diagnostic workup. The reason for this high abandonment, despite good disease prognosis, is a relevant social and health issue, and needs further evaluation. The problems discussed in this study are relevant to lower-income families and areas where health care is not easily accessible. The government agencies, nongovernment organizations and society would need to work together to overcome these issues.

Keywords

- childhood acute leukemia
- treatment abandonment
- incidence

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Introduction

Worldwide, acute leukemia (AL), especially acute lymphoblastic leukemia (ALL) is the commonest childhood cancer and also among the most treatable cancers in childhood (5-year survival rate for children >90% in many developed countries).^{1,2} There have been no significant real-life data from the eastern part of India. Saikia et al from Northeastern India have shown in their study that poor socioeconomic status in addition to the presence of higher proportions of disease-related risk factors in children with ALL leads to poor outcome in this part of the country.³ It has been observed, that though this is one of the most treatable childhood cancers, many children were unable to complete protocol-based therapy. By understanding the pattern of childhood AL at our tertiary care center and the abandonment rates among diagnosed children, prior to completion of diagnostic workup, we aim to understand the reason(s) for such abandonment.

Materials and Methods

This is a retrospective analysis from an ongoing registry of AL patients in the pediatric age group attending our hospital which spanned from June 2014 to November 2017. The sample size is 710. Most of our patients are referred from other hospitals where there is no proper hematology or oncology department. Children mostly had complaints of fever, pain all over body, or lethargy with occasional transfusion requirements. AL was diagnosed based on peripheral smear examination of blood at the outpatient department (OPD), and subsequently the bone marrow study and immunophenotyping (IPT) was done to confirm the lineage. All childhood AL patients in the specified time period were included and meticulously traced from the case records, digital OPD records, and indoor patient treatment sheets. No randomization was done, as there was no therapeutic intervention monitoring.

Inclusion Criterion

All newly diagnosed AL patients up to 18 years of age, who attended the Hematology OPD at our Hospital from June 2014 to November 2017, were included.

Exclusion Criterion

We have excluded patients >18 years of age, patients having any history of treatment of AL outside our institute, and patients with relapsed AL. Pediatric patients with diseases, other than AL, were also excluded.

Simultaneously, all the patients were assessed in detail by the following:

- Clinical examination.
- Complete blood count and peripheral blood smear (PBS).
- Bone marrow (BM) aspiration and biopsy.
- IPT from bone marrow aspirate by standard procedure as per the Euronet Protocol for subcategorization into ALL, Acute Myeloid Leukemia (AML), Acute Promyelocytic Leukemia (APML), and Mixed Phenotypic Acute Leukemia (MPAL).

- Cytogenetics from bone marrow aspirate and molecular studies from peripheral blood.
- Baseline serology for Human Immunodeficiency Virus (HIV) 1 and 2, anti-Hepatitis C virus (HCV), and complete Hepatitis B profile were done for all patients.
- Molecular studies for AML, APML, ALL were sent for all patients by Polymerase chain reaction (PCR) or Fluorescence in-situ Hybridization (FISH)-based methods, but we have not done Next-generation sequencing (NGS) due to logistic issues.

In addition to all the above variables, the demographic details of the patients, their socioeconomic status, and distance travelled to reach our hospital were recorded. Every patient with childhood AL was accompanied by their parents, elder siblings, and other responsible guardians. There was no problem in getting their local address as following details were always noted in our institutional records, such as village, post office, local police station, district and state. Besides, mobile phone numbers of responsible guardians were also saved in our registry, so that we could retrieve any missing data. Our hospital is located in Kolkata which is the largest metro city from Eastern part of India. Hence, the approximate distance travelled were estimated for all patients by measuring the average distance of each district from Kolkata (where our center is located), taking our center at Kolkata as the starting point.

The duration of study was from June 2014 to November 2017, that is, 3 years and 5 months. As this was an ongoing study process, simultaneous inclusion and follow-up were done for each patient during the study period. The end points of our study were (1) before starting definitive therapy at our center, and (2) before arriving at a definitive subtyping of leukemia.

Statistical Analysis

The data has been analyzed after digitization with the help of the EPI Info and R Software (R 3.5.1 software) in graphical fashion. The frequency of patients with their mean, median, and range variables was analyzed in nominal fashion and subsequently percentages were calculated.

The graph was constructed using igraph software package (Gabor Csardi and Tamas Nepusz. [2006], <https://igraph.org/>) for complex network research in R (R Core Team. [2020]; R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. <https://www.R-project.org/>). The graph we constructed is an undirected acyclic graph where symptoms were considered as nodes. All co-occurring symptoms were connected using an undirected edge. The 95% confidence interval (CI) was computed on the co-occurring phenotypes, all edges of the graph were extracted and a one-sample *t*-test was performed on the edge counts using igraph in the R statistical software.

Ethics

All the procedures and analyses followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Ethics Committee Approval was obtained from the Institutional Ethical Committee, Nil Ratan

Sircar (NRS) Medical College, Kolkata, West Bengal, India, vide order No./NMC/551 and dated February 4, 2020. The consent waiver was obtained from the Ethics Committee due to the retrospective nature of the study.

Results

During the study period, the total number of pediatric patients diagnosed with AL from peripheral blood at our Hematology OPD was 710. The median age of patients was 11 years (range: 2 months–18 years), and there was a male preponderance (1.7:1). The most common group of patients was aged 1 to 10 years (median age: 5 years). On history taking and clinical examination, fever in 478 (67.4%) patients was the commonest complaint, followed by pallor in 274 (38.6%). Bleeding manifestations were seen in 82 (11.5%), bone pain in 98 (3.8%), lymphadenopathy in 106 (14.9%), testicular enlargement in 8 (1.1%), and superior vena cava syndrome in 7 (0.9%) patients. Many patients had one or more symptoms. In ►Fig. 1, the co-occurring symptoms have been highlighted graphically. The co-occurring symptoms with 95% CI are as follows (►Fig. 1): infection pallor, fever infection, pallor swelling, pallor weakness, fever body ache, pallor hepatosplenomegaly, bleeding pallor, fever swelling, fever bleeding, fever weakness, and fever pallor.

The results of the *t*-test were significant: *t*-statistics value = 3.6129, degree of freedom = 99, *p* = 0.0004779, mean of population: 10.68, 95% CI: 4.814445–16.545555.

The mean hemoglobin (Hb), mean total leukocyte count (TLC), and mean platelet count were 7.9 g/dL (range: 1.9–11.8 g/dL), 32,655/mm³ (range: 200–300,000/mm³), and 76,187/mm³ (2,000–800,000/mm³), respectively (►Table 1).

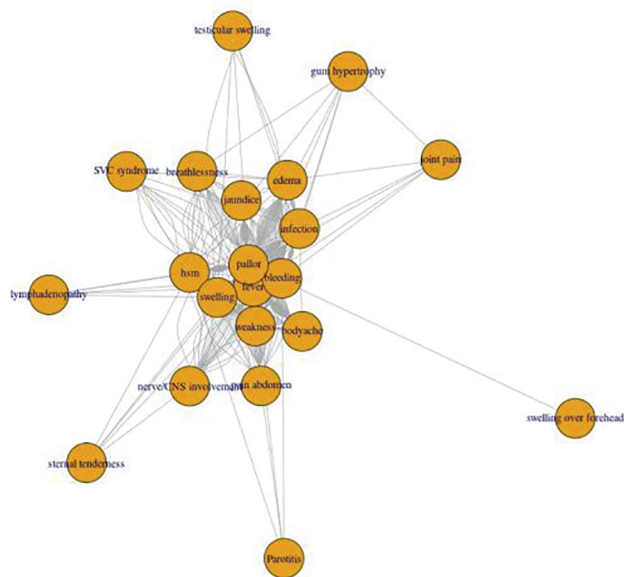


Fig. 1 Graphical representation of presenting symptoms in patients with acute leukemia. Many patients had multiple symptoms during presentation. These cooccurring symptoms have been depicted in a graphical fashion. All patients having only one symptom have been removed from this depiction. Each symptom is considered as a node. hsm, hepatosplenomegaly; SVC, superior vena cava syndrome.

The abandonment rate of AL patients at our OPD after initial visit was 250 (35.2%). Subsequently, among patients who continued with further evaluations, as mentioned in “Material and Methods,” precursor B-cell (Pre-B) ALL in 307 (43.2%), early Pre-B ALL (Pro-B ALL) in 10 (1.4%), T-cell ALL (T-ALL) in 51 (7.1%), AML in 45 (6.3%), APML in 28 (3.9%), and MPAL in 19 (2.6%) were diagnosed (►Table 1).

Out of 710 pediatric AL patients, 460 (65.8%) patients were further subcategorized with the help of IPT conducted on blood or bone marrow aspirate and subsequently treated. After the initial visit, 250 (35.2%) patients did not return for subsequent investigations or treatment. Age-wise distribution of patients who subsequently did not follow-up in the groups of <1 year, 1 to 10 year, and >10 to 18 years was 19 (7.6%), 139 (55.6%), and 92 (36.8%), respectively. Among 460 pediatric patients of AL, who were subsequently evaluated and treated 239 (51.9%), were in the age group of >10 to 18 years with Pre-B ALL being the commonest subtype among all age groups (►Fig. 2).

We analyzed the distances travelled by patients and their accompanying persons in detail. We found that the least distance travelled by patients was from the adjoining district, Howrah, that is, 16 km, and this is 5% of all the patients. Another interesting observation was that approximately 38%

Table 1 Depiction of the baseline parameters of patients with acute leukemia

Total number of acute leukemia patients (n = 710)	
Median age (range)	11 years (2 months–18 years)
Sex (male:female)	510:200 (1.7:1)
Fever	478 (67.4%)
Pallor	274 (38.6%)
Bleeding manifestations	82 (11.5%)
Bone pain	98 (13.8%)
Lymphadenopathy	106 (14.9%)
Testicular enlargement	8 (1.1%)
Superior vena cava syndrome	7 (0.9%)
Mean Hb in g/dL (range)	7.9 (1.9–11.8)
Mean TLC in /mm ³ (range)	32,655 (200–300,000)
Mean Platelets in /mm ³ (range)	76,187 (2,000–800,000)
Acute leukemia (not further evaluated; abandonment rate)	250 (35.2%)
Pre-B ALL	307 (43.2%)
Pro-B ALL	10 (1.4%)
T-ALL	51 (7.1%)
AML	45 (6.3%)
APML	28 (3.9%)
MPAL	19 (2.6%)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; Hb, hemoglobin; MPAL, mixed phenotypic acute leukemia; Pre-B ALL, precursor B-cell acute lymphoblastic leukemia; Pro-B ALL, early Pre-B ALL; T-ALL, T-cell ALL; TLC, total leukocyte count.

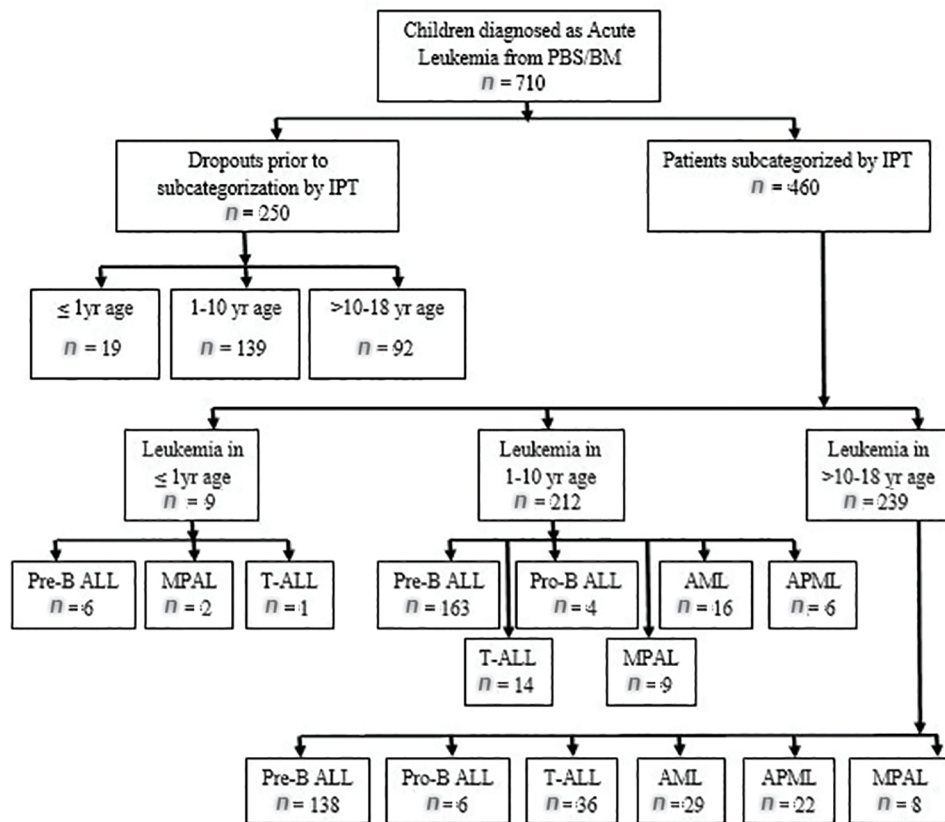


Fig. 2 Age-wise distribution of acute leukemia patients. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; BM, bone marrow; IPT, immunophenotyping; MPAL, mixed phenotypic acute leukemia; PBS, peripheral blood smear; Pre-B ALL, precursor B-cell ALL; Pro-B ALL, early precursor B-cell ALL; T-ALL, T-cell ALL.

patients travelled distances more than 500 km to visit the Haematology OPD at our center. Majority of our patients have travelled distances between 100 and 200 km, and this comprises approximately 47% of all patients. The mean distance travelled by all these pediatric patients with AL was 161.66 km (0–1,186 km) from their respective homes to our Haematology OPD located at Kolkata (► **Fig. 3**). On analyzing the travel pattern of the patients, the maximum distance travelled by patients for completing treatment was 618 km, average distance being 118.9 km. All the patients who completed treatment were from the state itself, implying better compliance.

Patients of pediatric AL can get admitted on 2 days per week at our Haematology OPD. The number of beds available per OPD for admission is on an average 3. The mean turnaround time of bone marrow procedures, and other needful investigations sent along with, i.e. IPT, and cytogenetics were 5 (1–6), 6 (1–7), and 10 (9–14) days, respectively. Molecular studies were sent from peripheral blood, and turnaround time on an average is 14 (12–18) days (► **Fig. 4**).

Discussion

This study was primarily undertaken to get an overall impression about pediatric AL from Eastern India, with a balancing

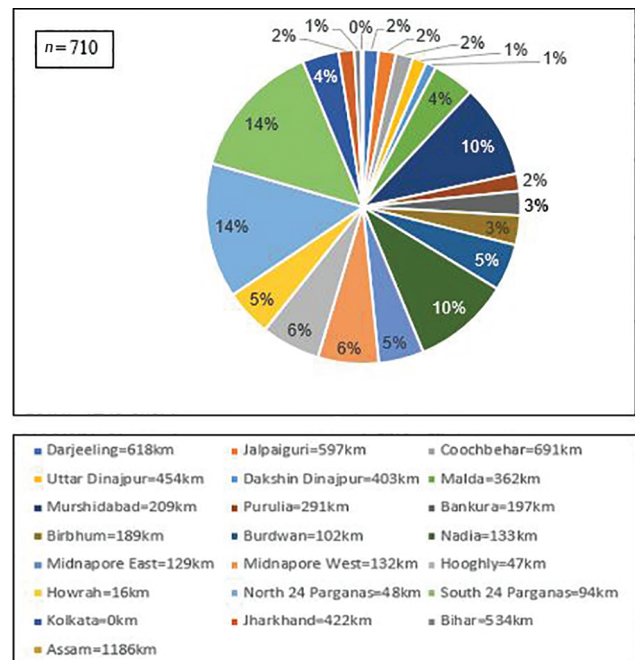


Fig. 3 Approximate distance travelled by the patients to attend the Haematology OPD. The distance travelled by each patient was assessed by calculating the average distance between Kolkata and the respective districts (of West Bengal) or states (of India).

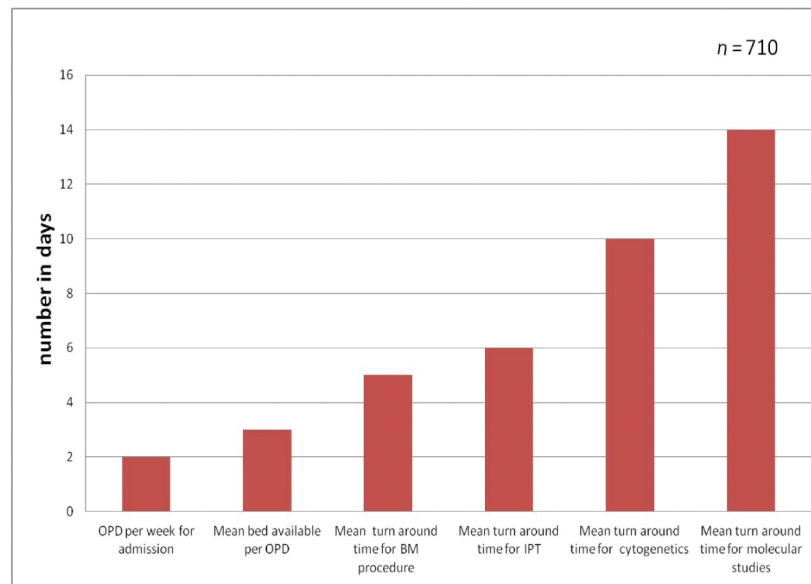


Fig. 4 Turnaround time of various procedures of acute leukemia patients (expressed in days). BM, bone marrow; IPT, immunophenotyping; OPD, outpatient department.

act of science and actual scenario, because of dropouts after initial OPD visits. Thus, a single-center data audit was performed to study various parameters in the population contacting us for treatment. Few studies are available from Eastern India, with one from Northeastern India, representing data in 73 patients.³ A study was reported by Mukhopadhyay et al from Eastern part of India with 500 pediatric patients of AL, but it has not mentioned drop outs.⁴

A male preponderance was observed, and the median age was 11 years which is similar with most of the studies on pediatric ALL. Study conducted at Hyderabad, Telangana, India, presented data of 103 patients.⁵ The most common pediatric AL detected was Pre-B ALL. The commonest clinical presentations were fever and pallor. In India, leukemia contributes to 25 to 40% of all childhood cancers, and majority, that is, 60 to 80% is ALL. AL in children is associated with male preponderance.⁵⁻⁸ Foà et al, in his analysis of a large cohort of patients, had highlighted a peak in the incidence of ALL in the age groups 1 to 5 and 5 to 10 years, with a progressive decrease from 10 to 30 years. Interestingly, gender distribution highlighted an overall lower incidence of females.⁹ In our study, the commonest symptoms of the patients diagnosed with AL, were fever and pallor, followed by bone pain and lymphadenopathy. In studies by Siddaiahgari et al and Biswas et al, the commonest findings were fever and pallor.^{5,10} Khalid et al have found lymphadenopathy and hepatomegaly as the most common initial findings.¹¹

In a study by Biswas et al, incidence of ALL was 72%, followed by AML with an incidence of 18.7%.¹⁰ This was also similar in our study with ALL (84%) and AML (16%) among 460 patients, after IPT reports. As assessed by Siddaiahgari et al, Pre-B ALL was the commonest (82.44%), and T-ALL was noted in 15.46% patients.⁵ Study by Philip et al, from CMC Vellore, have found incidence of AML of 12.3% among ≤15 years' age group.¹²

The important aspect of our study analysis was that 250 (35.2%) pediatric patients with AL dropped out after the first visit to our OPD. International Society of Pediatric Oncology (SIOP) defines abandonment as refusal to begin curatively intended treatment after diagnosis, or abandonment after initiating treatment, or absence of 4 weeks or more during treatment.¹³ The abandonment rate of pediatric cancers from low- and middle-income countries (LMIC) is as follows: Kenya, 54%; Zambia, 45%; and Indonesia, 48%.¹⁴⁻¹⁶ A sincere attempt was made to trace down the exact cause by cell phone contact number but most patient relatives and parents were not particular about any reason, sometimes even the cell number provided was inaccurate and some stayed in very remote areas, making it difficult to contact them. A complex interplay of biological-, socioeconomic-, and treatment-related factors underlies this problem.¹⁷

The distance travelled by each patient was assessed by calculating the average distance between Kolkata and the respective district or state. Few patients had to travel approximately 700 km; however the average distance travelled to reach the Haematology OPD was 161.66 km. We cannot exactly pinpoint the distance travelled for treatment drop out, but many patient relatives do not have proper logistics at Kolkata and this could be a major factor for the patients not attending the hospital for a second visit. A Zambian study stated that long travel distance to the hospital and low educational level of the mother significantly correlated with a higher risk of abandonment.¹⁶ In a study by Hazarika et al, from Northeast India, out of 592 childhood cancer patients, approximately 23 (3.9%) patients refused treatment. The reasons for treatment refusal were found to be long travelling distance from the area of residence to treatment center in 11 (47.8%) patients and poor financial status in 6 (26.1%) patients.¹⁸

It is possible that patient may have attended another private or government hospital for further treatment. Although

the treatment at our government medical center is relatively free, multiple visits to the hospital and long duration of stay may not be financially feasible for the patient's family as, sometimes, the father is the only earning member in the family. There may be elderly dependents and other younger children at home, who face social and economic issues, in absence of parents, who have to stay with the affected child in or around the vicinity of the hospital for receiving treatment.

In view of high patient attendance at our OPD, not all patients can be accommodated immediately for admission at the Haematology indoor. AL in the pediatric patients is our top priority and despite early preferences, the average turnaround time for needful investigations cannot be less than a week as mentioned in ►Fig. 3. In the interim period, patients are advised for both supportive and emergency care from pediatric department of our hospital or from their local hospital. The turnaround time for all the required investigations for AL in our department is in accordance with the international guidelines.¹⁹ Patients with a suspicion of APML, however, are usually admitted on a priority basis at our center, and treatment initiated immediately. Treatment is started as soon as there is a suspicion of abnormal promyelocytes in the peripheral blood smears. Simultaneously, FISH for promyelocytic leukemia/retinoic acid receptor α (PML-RARA) is also sent from blood (turnaround time of 48–72 hours). The turnaround time of the rest of the investigations is same as for the rest of the ALs.

Another important consideration prior to the treatment of a disease, such as AL, is proper counseling of the patient and, in case of the pediatric patients, their relatives, to decrease the rate of abandonments.²⁰ However, in a tertiary government hospital with huge number of patients, doctor–patient interaction time is often inadequate. The doctor–patient ratio in our OPD is approximately 1:35. The study by Sengar et al, from our country, has noted that Indian medical oncologists (MO) have higher clinical volumes and workload than MOs in other LMICs and substantially higher workload than MOs in high-income countries.²¹ For this reason, several volunteer organizations and counselors are employed for adequate patient counseling.

A study by Friedrich et al, from a global survey in pediatric cancer patients, mentioned about emerging factors including vulnerability, family dynamics, perceptions, center capacity, public awareness, and governmental health care financing as other important issues to be addressed.²²

Limitations

The limitation of our study is that we were unable to follow-up the patients who could not be diagnosed further at our center. This would have further shed light on whether they have been subcategorized or received therapy elsewhere. To be able to follow-up the patient till the end of therapy would accurately highlight the reasons for treatment abandonment and also give a truer picture of the disease outcome. A larger population should be followed-up for filling this void.

Conclusion

Identifying the potential problem areas which led to treatment abandonment can help us in managing the same and thus, ultimately lead to more and more children being treated and becoming disease free. The problems discussed in this study are relevant to lower-income families and areas where health care is not easily accessible. The government agencies, non-government organizations, and society as a whole would need to work hand in hand to overcome these issues.

Authors' Contributions

This work was carried out in collaboration with all authors. Author AS collected the data, analyzed the data and wrote the manuscript. Authors PC and SNB analyzed the data and reviewed the manuscript. Author AKT did the statistical analysis. Authors PKM, RD, TKD helped in patient care. Author SD helped in laboratory diagnosis of AL and its subtypes.

All authors read and approved the final manuscript.

Source of Funding

None.

Conflict of Interest

None declared.

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