Article published online: 2022-09-01

Pediatric Acute Myeloid Leukemia in India: A Systematic Review

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Ind J Med Paediatr Oncol 2022;43:342–348.

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Abstract

Background Lower-middle-income countries face unique problems in the management of pediatric acute myeloid leukemia (AML) due to which the outcomes have not kept pace with developed nations. In India, data on childhood AML is sparsely available, thus making a true assessment of disease trends difficult. The current systematic review was undertaken to assess the outcomes of childhood AML from published literature from India over a period of 10 years (2011–2021).

Materials and Methods A systematic search of MEDLINE, Google Scholar, and SCOPUS was performed as per preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement from January 1, 2011 to December 31, 2021. In addition, International Society of Pediatric Oncology (SIOP) conference abstracts were also screened for relevant studies on AML from India. This study was registered in PROSPERO (ID42021273218).

Results A total of 1,210 patients from 19 studies were included. Standard 3 + 7 and MRC AML based regimens were commonly adopted regimens for induction. Remission rates varied between 56 and 95%. Overall treatment-related mortality across studies was 23.2% (95% confidence interval [CI]: 10.3–35.9%). The mean incidence of treatment abandonment was 19.3% (95% CI: 10.9–27.5%). Event-free survival and overall survival were in the range of 28 to 55% and 15 to 66%, respectively. Hematopoietic stem cell transplantation was performed only on a small subset of patients.

Conclusion Outcomes of pediatric AML in India continue to be suboptimal with high treatment abandonment and toxic deaths. Ensuring uniform access to therapy and supportive care along with a robust social support system would improve outcomes of childhood AML in India.

Keywords
- acute myeloid leukemia
- India
- lower-middle-income countries
- abandonment

Introduction

Acute leukemia accounts for approximately one-third of all childhood malignancies, of which 15 to 20% cases comprise of acute myeloid leukemia (AML).[1] The outcomes of childhood AML in high-income countries (HICs) have currently surpassed 70% with an increased focus on targeted therapies to further these outcomes and also simultaneously reduce toxicity.[2,3] Lower-middle-income countries (LMICs) continue to have suboptimal outcomes due to various socioeconomic and disease-related factors.[3] There is limited data on childhood AML from India.[4] As a result, there is limited

DOI https://doi.org/10.1055/s-0042-1754370.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

understanding of disease trends, which may ultimately compromise patient care. A previous systematic review from India, which included studies published between 1990 and 2010, highlighted several shortcomings of managing pediatric AML.[5] The current systematic review was undertaken to study the treatment strategies and outcomes of pediatric AML in India. The review included studies published between January 1, 2011 and December 31, 2021.

Materials and Methods

Protocol and Registration

This systematic review was registered on PROSPERO (ID42021273218).

Eligibility Criteria

Inclusion Criteria

1. Studies reporting on pediatric AML in India.
2. Studies written in English.
3. Prospective, retrospective, and ambispective studies.

Exclusion Criteria

1. Studies on pediatric AML not from India.
2. Case reports, reviews, and books.

Settings

There were no restrictions on the type of setting in which the studies were conducted.

Information Source

A systematic search of the MEDLINE, Google Scholar, and SCOPUS database for published studies on pediatric AML from India was conducted. In addition, SIOP conference abstracts were also screened. The reference lists of the included studies or relevant reviews were screened for other eligible studies.

Time

Search of database was from January 1, 2011 till January 31, 2021. SIOP conference abstracts were screened from year 2011 to 2020.

Literature Search

A comprehensive literature search was performed using text words "Acute myeloid leukemia," "AML," "child*," "India." Articles published in English alone were reviewed. Literature search was as per preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. The full search strategy is shown in **supplementary material.**

Study Selection

Two review authors (S.S and V.R.M.G) independently screened the titles and abstracts yielded by the search against the inclusion and exclusion criteria. Full reports for all titles and abstracts were obtained if they appeared to meet the inclusion criteria and in case of any uncertainty. Review authors then screened the full text reports and decided whether the inclusion criteria were met. If necessary, additional information from study authors was sought to resolve questions about eligibility and disagreement was resolved through discussion. Reasons for excluding trials were also recorded. None of the review authors were blinded to the journal titles or to the study.

Data Collection Process

Data extraction from the included studies was performed using standardized data collection forms. Two reviewers (S.S and N.D) independently extracted the data to reduce the bias and errors in data extraction and the studies in question were jointly reviewed by the two investigators and the final determination was reached by consensus.

Data Items

The information that was extracted from each study included surname of the first author, year of study, median/mean age with range, number of patients, chemotherapy administered, induction mortality, complete remission (CR) rate, duration of follow-up, relapse, event-free survival (EFS), overall survival (OS), treatment-related mortality (TRM), treatment abandonment, prognostic factors, and use of hematopoietic stem cell transplant (HSCT).

Evaluation of Quality and Risk of Bias

Quality was assessed by two authors using the quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.[6]

Synthesis Method

All studies included were screened for the required data items and results were tabulated using Microsoft Word software. Categorical variables were expressed as the number of cases and percentages (%). Mean along with 95% confidence interval (CI) was calculated to report the incidence of TRM and abandonment rates. Statistical analyses were done using the R software version 4.0.2.

Results

Literature Search

A total of 1,057 studies and 15 SIOP conference abstracts were obtained after the initial search. Additionally, seven other studies were added after citation searching. After removing duplicates and screening the titles and abstracts of the publications, full text of 60 studies were assessed of which 19 were included for the systematic review. The PRISMA flowchart is shown in ►**Fig. 1**.

Quality of Studies

The quality assessment tool for observational cohort and cross-sectional studies from the National heart, Lung, and Blood Institute of the National Institutes of Health was adapted to assess the quality of included studies (►**Supplementary Table S1**).[7] Overall, the quality of the study was poor in 1 (5%) study, fair in 8 (42%) studies, and good in

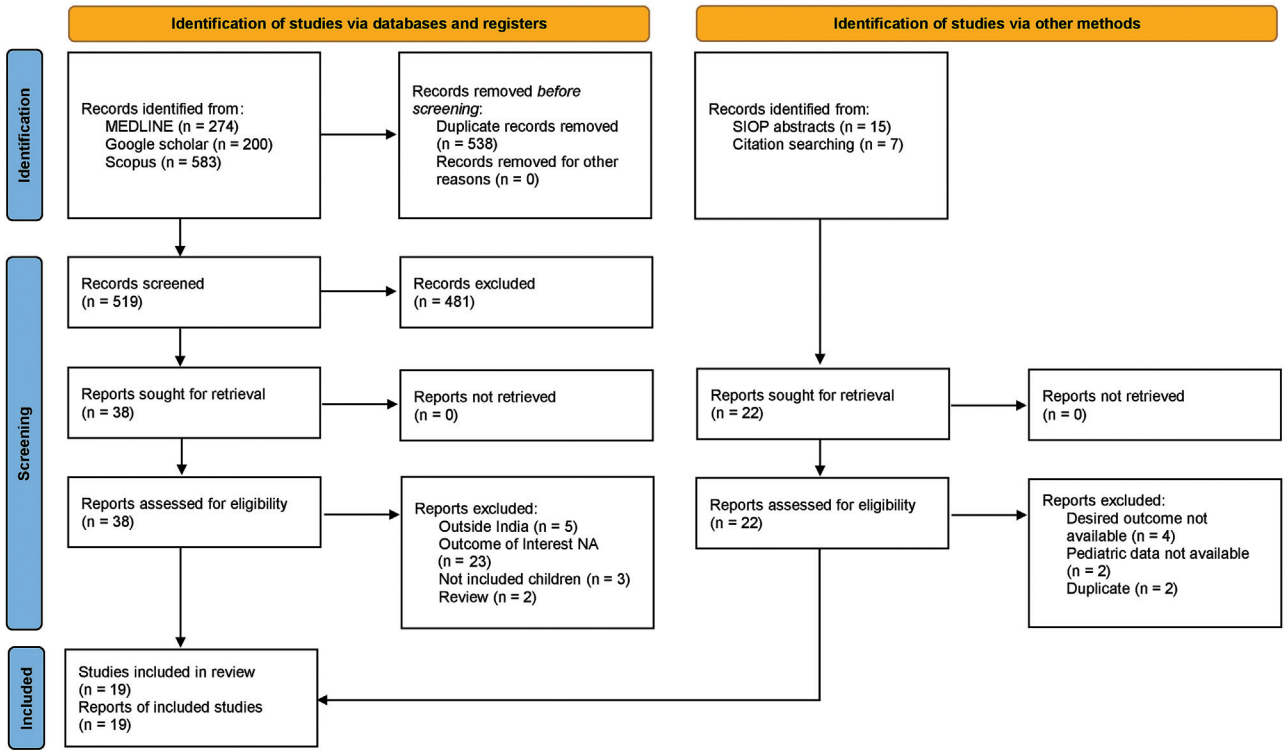

Fig. 1 Flow diagram of the systematic review according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

10 (53%) studies of the 19 studies included in the systematic review.

Characteristics of the Studies

A total of 1,210 patients were included from the 19 studies.[8–26] Three of the 19 studies also included patients with acute promyelocytic leukemia (APML).[19,21,22] Eight studies were published before 2015, while the remaining 11 studies were published in or after 2015. The various studies included patients between 1 and 19 years of age. There was slight predominance of males across majority of the studies. The salient features of the studies are summarized in ►**Table 1**.

Data regarding induction chemotherapy were available from 17 studies.[8,9,11–23,25,26] Anthracycline-based regimens were used for induction in all studies. 3 + 7 regimen consisting of daunorubicin (45–60 mg/m^2/day) and cytarabine (100–200 mg/m^2/day) was the standard regimen used in nine studies, while MRC AML based regimens that included an additional third agent (etoposide) were used in seven studies. In another study, patients were treated with AML-Berlin-Frankfurt-Munich (BFM) 98 protocol in which idarubicin was the anthracycline used. CR rate was available from 11 studies and varied between 56 and 95%, and overall there was no major difference in CR rates between 3 + 7 regimens (56–78%) and MRC-based regimens (64–95%)[7,9–11,13,14,16–18,20,22]. Six of the 17 studies used maintenance chemotherapy.[13,14,16,20,21,26] Six studies mentioned regarding HSCT (Reference: 8,9,16,17,22,25). A total of 20 patients underwent HSCT in these studies, 15 in CR1 and another 5 in CR2.[8,9,16,17,22,25] Overall induction mortality (10 studies) and TRM (9 studies) were 12% (95% CI: 6.4–17.8) and 23.2% (95% CI: 10.3–35.9), respectively.[7–9,12–20,22,24,25] Only three studies had a TRM of less than 10%, while four other studies had a high TRM over 20%.

Duration of follow-up was available from seven studies and the shortest and longest follow-up period was 7 and 31 months, respectively.[11,12,14,16,22,26,27] Data pertaining to event-free survival/disease-free survival (EFS/DFS) was available from 10 studies.[8,11,12,14,17–20,23,26] The overall EFS/DFS reported among these studies ranged between 28 and 52%. Data for OS was available from 16 studies.[8–11,13–21,23–25] Philip et al reported an OS of 70% with a follow-up of 7 months. Remaining 15 studies had OS ranging between 15 and 66%. In general, the OS of studies that used maintenance therapy (19–66%) was not different from those studies that did not offer maintenance (15–55%). Prognostic factors could be determined from four studies.[8,12,17,21] High-risk cytogenetics that included -5/del 5q, -7/del 7q, complex cytogenetics (defined as more than 3 structural and/or numerical abnormalities) were cited to have negative impact on CR and relapse rate. Sharawat et al highlighted the negative impact FMS-like tyrosine kinase 3 - internal tandem duplication (FLT3-ITD) mutations (DFS of 18% for FLT3-ITD-positive vs. 51% for FLT3-ITD-negative patients).[12] Kapoor and Yadav in their paper highlighted that the negative impact of adverse cytogenetic/molecular can be negated by HSCT in CR1.[22] The mean incidence of treatment abandonment that was available from 11 studies was 19.3% (95% CI: 10.9–27.5).[7–10,12,17,18,20–23] Six (55%) of these studies reported an abandonment rate over 20%.

Table 1 Characteristics of 19 studies included in the systematic review

Study	Type of study	Time period	Age (in years)	M:F ratio	Number of patients	Chemotherapy	Risk group included	Median follow-up	Abandonment (%)	CR (%)	Relapse/ refractory disease (%)	EFS/DFS	Induction mortality (%)	Overall TRM (%)	OS
Gupta et al 2011 [8]	Retrospective	2005–2009	Mean: 12.4 (1–18)	1.9:1	35	In-I: 3 + 7 (D45mg/m2 + Arac 100mg/m2) In-II: HAM Consol: HIDAC	All	NA	5.7%	77.1%	40%	2 years DFS: 40%	2.9%	5.7%	NA
Yadav et al 2011 [9]	Retrospective	2005–2010	NA	NA	51	UKAML12 protocol	All	NA	55%	NA	26%	NA	22%	48%	26%
Mohammed et al 2013 [10]	Retrospective	2006–2013	NA	NA	34	NA	All	NA	26%	56%	26%	NA	12%	NA	59%
Kota et al 2013 [11]	Retrospective	2007–2012	1–19	1:6:1	63	In: 3 + 7 Consol: NA	NA	11 months	21%	78%	NA	Median EFS: 11 months	NA	NA	3 year OS: 15%
Sharawat et al 2014 [12]	Retrospective	2008–2010	Median: 10(1–18)	3:1	64	In: 3 + 7 (60mg/m2 *3 days) Consol: HIDAC	All	18.3 months	NA	83%	NA	EFS: 30.2 ± 5.8% DFS: 43.03 ± 7.3%	NA	NA	37.1 ± 6.3%
Jain et al 2014 [13]	Retrospective	2000–2013	NA	NA	88	In: 3 + 7 & 5 + 2 Consol: HIDAC + M	NA	NA	34%	NA	NA	NA	NA	18%	NA
Jayabose et al 2014 [14]	Retrospective	2010–2014	NA	0.9:1	39	Modified MRC-10 protocol + M	All	29 months	NA	72%	21.4%	3 year EFS: 40%	NA	18%	3 year OS: 47.5%
Siddaiahgari et al 2014 [15]	Prospective + Retrospective	2009–2012		0.7:1	32	UK AML 15 protocol	All	NA	NA	94%	16%	NA	NA	6%	72%
Philip et al 2015 [16]	Retrospective	2012–2014	NA	NA	23	AML-BFM 98 protocol + M	NA	7 months	NA	NA	NA	NA	17%	NA	1 year OS: 70.4 ± 10.7%
Radhakrishnan et al 2015 [17]	Retrospective	2008–2013	Median: 9 (1–17)	2.25:1	72	In: DAE/DA Con: HIDAC	All	11.7 months	NA	72%	NA	EFS: 28%	5.5%	7%	OS: 36%
Ramamoorthy et al 2015 [18]	Retrospective	2004–2013	Mean: 7.3 ± 3.6	3.2:1	100	AML MRC 12 protocol	All	NA	3%	64%	25%	DFS: 34.7%	25%	48%	27.2%
Seth et al 2016 [19]	Retrospective	2011–2015	Median: 7.5 (1.5–13)	NA	71 (Included APML)	MRC-10 protocol	All	NA	25%	95% (excluding APML)	NA	3 year EFS: 43% (excluding APML)	5.4%	27%	3 year OS: 55% (excluding APML)
Narula et al 2017 [20]	Retrospective	2011	NA	NA	65	In: 3 + 7 Consol: HIDAC + M	All	NA	NA	NA	NA	3 year DFS: 66% 3 year EFS: 49%	<20%	NA	3 year OS:66%
Naseer et al 2017 [21]	Retrospective	2012–2017	NA	2:1	42 (included APML)	In: 7 + 3 and 5 + 2 Con: HIDAC + M	All	NA	9.4%	56%	25–28%	NA	18%	NA	19%
Kapoor et al 2018 [22]	Retrospective	2015–2018	NA	NA	24 (Included APML)	In: 3 + 7 Consol: HIDAC	All	31 months	4%	NA	29%	NA	NA	NA	67%
Peyam et al 2018 [23]	Retrospective	2011–2017	Mean: 6.96(1–12)	2.2:1	114	MRC 15 protocol	All	NA	8.8%	67.5%	22.8%	3 year EFS: 31.6%	NA	30.7%	NA
Sinha et al 2019 [24]	Retrospective	2014–2015	<15	1.7:1	65	NA	NA	NA	20%	NA	NA	NA	NA	NA	36.9% at 5 months after diagnosis
Uppuluri et al 2020 [25]	Retrospective	2002–2019	8	NA	48	MRC 15 protocol	All	NA	NA	NA	41%	NA	6.2%	NA	5 year OS:53%
Srinivasan et al 2020 [26]	Retrospective	2014–2017	9	NA	180	Upfront OMCT f/b 3 + 7 and HIDAC + M	All	25 months	NA	NA	NA	2 year EFS: 46–52	6.5%	NA	2 year OS: 47–53%

Abbreviations: APML, acute promyelocytic leukemia; AraC, cytarabine; consol, consolidation; CR, complete remission; DAE, Daunorubicin, Cytarabine, Etoposide; Dauno, daunorubicin; DFS, disease-free survival; EFS, event-free survival; f/b, followed-by; HAM, high-dose cytarabine, mitoxantrone; HIDAC, high-dose cytarabine; In, induction; M, maintenance; M:F, male:female; NA, not available; OMCT, oral metronomic chemotherapy; OS, overall survival; TRM, treatment related mortality.

Discussion

Treatment of AML in children continues to remain a challenge in LMICs. A previous systematic review published by Kulkarni and Marwaha in the year 2010 summarized two decades of experience of treating pediatric AML in India.[5] Their review included 322 children between the year 1990 and 2010, which is much smaller than our current review that included 1,200 children treated over a shorter duration of 10 years. Also, a recent systematic review on pediatric AML from LMICs acknowledged that maximum data was contributed from India.[3] This is a step in the right direction indicating that more Indian children with AML are being treated and reported. But, the true incidence of childhood AML in India is unknown. According to World Health Organization, the estimated number of new cases of leukemia from India, in the 0 to 14 age group, for the year 2020 was 11,850 and considering that approximately 15% of these patients have AML, the annual incidence of childhood AML should be approximately 1,750.[28] Thus, there continues to be underreporting and underdiagnosis of pediatric AML in India.

Treatment abandonment is a major hurdle and is one of the most common reasons for treatment failure in LMICs.[29] In fact, treatment abandonment is thought to contribute to at least a third of the survival difference between HICs and LMICs.[30] Though not systematically reported, the current review highlights an alarmingly high abandonment rates among children with AML, with no major improvements in comparison to previous reports.[5] Perceived prognosis of the disease, cost of treatment, and concerns of toxicity are few of the contributing factors to such high abandonment rates. Studies from India and other LMICs have highlighted that a comprehensive support group consisting of clinicians, as well as existing non-governmental organizations and governmental organizations can significantly reduce abandonment.[31–33]

TRM is the next biggest hurdle in the treatment of pediatric AML in LMICs. The standard of care for pediatric AML continues to be anthracycline-based induction followed by three to four cycles of consolidation. Most of the chemotherapy protocols for treating pediatric AML in India have been adopted from HICs, but the lack of essential supportive care and option of intensive care unit admission, which are considered to be indispensable during intensive AML treatment, have led to survival gap in comparison to HICs. For example, Yadav et al highlighted a very high TRM of 48% when treated with the UKAML12 protocol.[9] On the contrary, the original UKAML12 trial that used the same protocol had a TRM of only 10%.[34] Similar to previous studies from India, the current review estimated a high incidence of induction mortality (12%) and overall TRM (23%), which is much higher compared with 5 to 10% occurring in HICs.[4,5,35–37] High rates of infection with multidrug-resistant organisms, invasive fungal infections, and poor nutritional status have led to poor tolerance and subsequently a high TRM during intensive chemotherapy. Uppuluri et al highlighted that early intervention by the pediatric intensive care team and granulocyte transfusion positively impacts survival.[25] For patients in resource-limited settings with level two facilities, SIOP Pediatric Oncology in Developing Countries (PODC) guidelines recommend an alternative strategy, to begin treatment with inexpensive, low-intensity oral chemotherapy followed by low-dose or standard-dose induction to reduce TRM and abandonment.[38] For patients with baseline adverse host-related factors, use of upfront low-dose oral chemotherapy as a bridge to intensive chemotherapy has been shown to be safe and reduce TRMs with comparable outcomes to those who directly receive intensive chemotherapy.[26] Another modifiable factor that contributes to TRM is malnutrition. The reported incidence of malnutrition among Indian children with leukemia is approximately 50%.[27,39,40] Promoting routine nutritional assessment and ensuring availability of nutritional supplements that are affordable and culturally appropriate, such as ready-to-use therapeutic foods, must be incorporated into the care of childhood leukemia in India.

Lack of uniform access and high cost contribute to low rates of HSCT in India. In the current review, HSCT rate was less than 2%. This remains a significant concern for a disease like pediatric AML in which a third of the patients are thought to be high risk and thus would qualify for HSCT in CR1. Also, patients from LMICs do not have access to many of the newer therapies such as antibody drug conjugates and small molecule inhibitors, which are currently available for AML. Incorporating a simple risk stratification, which will otherwise identify the favorable risk group who can be cured by chemotherapy alone, will be helpful, especially in the setting of limited access to HSCT. Identifying certain high-risk mutations such as FLT3 can be of therapeutic benefit in light of access to targeted therapies such as tyrosine kinase inhibitors.

The survival of pediatric AML in HICs has reached 70% and is mostly attributed to advanced diagnostic techniques, better supportive care, and improved salvage options including HSCT. This has not been the scenario in India and other LMICs where the OS ranges between 10 and 50%.[3] Compared with previous studies published in India, our current review shows no major improvement in survival trends in the past 30 years.[5] The lower survival rate in India can be attributed to high TRMs, high treatment abandonments, and low salvage rate after relapse. While the HICs continue to improve upon the benchmark survival of 70% through refinement of molecular risk stratification and increased efforts toward personalized targeted therapy approaches, the immediate steps in LMICs must address both socioeconomic and disease-related challenges as discussed.

The current systematic review has certain limitations. Of the 19 studies included, 9 studies were published only in abstract format and 3 studies included APML patients that are often analyzed as a separate subset. Certain characteristics including baseline comorbidities, risk stratification, and delay in diagnosis were not captured. The median follow-up time was not mentioned in majority of the studies and among those studies which mentioned it, three had a follow-up duration of less than 1 year.

Conclusion

In conclusion, the treatment outcomes of pediatric AML in India are substantially inferior compared with HICs. Lowering TRM and abandonments is of utmost importance. A holistic approach of including a social support team, intensified patient counselling, ensuring uniform access to cancer therapy and supportive care will go a long way in improving the outcomes of pediatric AML in India. Collaboration and prospective multicenter studies may not only ensure standard of care treatment but also reduce abandonment rates. The Indian Pediatric Oncology group (InPOG) initiative is a step in that direction.[41]

Other Information

Protocol registration: PROSPERO (ID42021273218).

Competing Interests

The authors do not have any competing interests to declare.

All data that have been collected for the purpose of this systematic review have been from published literature and are available in public domains.

Authors' Contributions

Shyam Srinivasan was involved in conceptualization, designing, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review.

Venkata Rama Mohan Gollamudi contributed to literature search and manuscript preparation.

Nidhi Dhariwal did literature search, data acquisition, and data analysis.

Conflict of Interest

None declared.

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