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RESEARCH

Treatment challenges and outcomes of older patients with acute myeloid leukemia from India

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Abstract

Globally, overall survival (OS) of older patients with AML continues to be suboptimal with very little data from India. In a multicenter registry analysis, we evaluated 712 patients with AML older than 55 years. Only 323 (45.3%) underwent further treatment, of which 239 (74%) received HMAs, and 60 (18%) received intensive chemotherapy (IC). CR was documented in 39% of those receiving IC and 42% after HMAs. Overall, 100 (31%) patients died within 60 days of diagnosis, most commonly due to progressive disease (47%) or infections (30%). After a median follow-up of 176 days, 228 (76%) of patients had discontinued treatment. At one year from diagnosis, 211 (65%) patients had died, and the median OS was 186 days (IQR, 137–234). Only 12 (3.7%) patients underwent stem cell transplantation. Survival was significantly lower for those older than 60 years ($p < 0.001$). Patients who died had a higher median age ($p = .027$) and baseline WBC counts ($p = .006$). Our data highlights suboptimal outcomes in older AML patients, which are evident from 55 years of age onwards, making it necessary to evaluate HMA and targeted agent combinations along with novel consolidation strategies to improve survival in this high-risk population.

Keywords AML · Leukemia · Cancer · Fungal · Chemotherapy

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Introduction

Recent progress in acute myeloid leukemia (AML) demonstrates significant age-related disparity, with most of the advances eluding older patients. Five year overall survival (OS) for patients older than 70 years of age continues to be less than 10%, even in high income settings. This represents a significant global challenge as the median age of presentation of AML is 68 years and approximately 30–40% patients are older than 75 years of age. challenge [1–4]. A significant proportion of patients do not receive curative treatment, and intensive chemotherapy (IC) is often precluded by co-morbidities or physiologic frailty. Although administration of intensive chemotherapy increases the rates of complete remission (CR), benefits are often mitigated by treatment related mortality or early relapses [5]. A significant proportion of patients receive treatment with hypomethylating agents (HMAs) alone, resulting in short overall survival [6]. Additionally, an increasing frequency of adverse molecular and cytogenetic abnormalities with age leads to higher rates of treatment failure irrespective of the intensity of therapy [7].

These challenges are further aggravated in resource limited settings such as India due to a higher risk of infections, lack of universal health care coverage, inadequate social support, cultural factors and early onset of physiologic frailty that hinder the administration of effective treatment [8]. The majority of treatment costs for AML are borne directly by patients, and access to therapy is often limited to a few centers requiring long distance travel [9]. Often, patients move to a different center or alternate systems of medicine, resulting in lack of robust data on long term outcomes and survival in this population [8]. Early onset of physiologic frailty is also evident on routine clinical practice in India, and it is uncommon for a patient above 60 years of age to receive IC with curative intent.

As a significant proportion of patients do not undergo detailed evaluation or treatment, there is dearth of data on epidemiology, patterns of care and outcomes of older patients with AML in India. This study was designed to analyze data from the AML registry of the Indian Hematology Cancer Consortium (HCC) with an attempt to describe the epidemiology, patterns of treatment and survival for AML among older patients. This data would facilitate development of optimal strategies to balance treatment efficacy and toxicity for older patients, keeping in context socioeconomic conditions in India and similar resource-constrained settings.

Patients and methods

Study design

This was a retrospective study including patients diagnosed with AML between 1stJanuary 2018 and 30th April 2021. Data was sourced from the AML registry of the Indian Acute Leukemia Research Database (*INwARD*) of the Hematology Cancer Consortium. This registry performs prospective data collection and has clearance by individual institutional ethics committees. The primary objective was to describe the proportion of patients receiving treatment. Secondary objectives were to describe treatment patterns, rates of complete response (CR), treatment related mortality, overall survival (OS) at one year from diagnosis and the impact of prognostic factors on survival. Survival and follow-up data were analyzed as of May 31, 2022.

Definition of 'older' patients

'Older' patients are variably defined based on cut-offs ranging from 65 to 70 years in various guidelines and clinical trials [10, 11]. Although the median age of onset of AML is approximately 68 years in published data, we selected a lower threshold of 55 years for this study [2]. This decision was based on previous data indicating a possibly lower median age of onset of AML in India [12]. Additionally, a substantial proportion of patients above 60 years of age do not receive intensive chemotherapy in Indian data, and a threshold of 55 years would be more representative of patients on the upper end of the spectrum undergoing treatment.

Diagnosis and work up

Due to the multicenter nature of this study, the specific procedures employed for baseline workup varied between institutions. However, all centers adhered to a general framework. Flow cytometry was performed on either peripheral blood or bone marrow aspirate samples for initial diagnosis. Conventional karyotyping and a limited AML panel by RT-PCR were mandatory for all patients, with a minimal detection of t(8;21), inv(16), and t(15;17). Detection of NPM1 or FLT3 mutations was implemented variably. Next-generation sequencing for AML-associated mutations was performed by individual centers based on their specific protocols.

Data collection and documentation

Patients were managed according to institutional protocols. Duringthe study period, the World Health Organization

(WHO) 2016 and European Leukemia Net (ELN) 2017 guidelines were utilized for classification and risk stratification, respectively [13]. Performance status was defined according to the European Cooperative Oncology Group (ECOG) scale. It was acknowledged that Venetoclax and FLT-3 inhibitors were not routinely available in India during the study period, and detailed information on the same was not available. Patients were classified into two groups, namely who underwent further evaluation and treatment (Group A) and those who did not (Group B).

The HCC is a collaborative group including institutions across India with an effort to generate large scale data pertaining to the treatment and outcomes of hematologic malignancies [14]. Data was collected using a secure online platform, and each center was responsible for maintaining the accuracy of their data. A dedicated Case Record Form (CRF) was completed and included details of demographics, clinical findings, bone marrow, cytogenetic and molecular data, type of treatment received, duration and responses to treatment, disease status at last follow up and survival status. Patients who were currently alive (on or off treatment) had details of their last follow-up recorded, including clinical and disease status. As patients could move from one center to another for treatment, duplicate entries from multiple centers were removed. To ensure data completeness and quality, source data verification was performed for all patients using physical or electronic documents by a central team of project managers.

Statistical analysis

Descriptive statistics, including mean and standard deviation for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data were used to summarize continuous variables. Frequency and percentage were used for categorical variables. The cumulative probability of survival was estimated using the Kaplan–Meier method for overall survival (OS) and event-free survival (EFS). The log-rank test was used to assess the impact of prognostic factors on survival. Study variables that were significant at levels < 0.05 in a univariate analysis were included in a multivariate Cox proportional hazards model. The model assumption was verified using log–log S(t) plots and a global test. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM Corp., Armonk, NY, USA)/SAS 9.4/STATA 16.

Results

Baseline data

A total of 750 patients were screened, of which 38 were excluded due to the non-availability of source documents for verification. In the remaining 712 patients, the median age was 63 years (IQR, 59–69) with a M:F ratio of 1.46. Only 323 (45.3%) patients received further treatment (Group A), while 389 (54.6%) did not initiate any further evaluation or treatment (Group B). A consort diagram of the study population is shown in Fig. 1. Both groups were similar in terms of age, co-morbidities, gender distribution and performance status. (Table 1) Other than a higher WBC count in Group B (median, 12150/mm3 vs 9640/mm3, $p = 0.037$), relevant baseline investigations were also similar. Baseline performance status was available for 638 (90%) patients, of which 280 (43.8%) had ECOG performance score 2 or worse and 386 (54.2%) had at least one long term co-morbidity. At diagnosis, 111 (34%) patients had clinical evidence of infections and required antimicrobial therapy within one week of starting treatment.

WHO classification and ELN risk stratification were specified for 585 (82%) and 409 (57.4%) patients, respectively. The most common disease subtype was AML-Not otherwise specified (AML-NOS) in 367 (62.7%) patients, followed by AML with myelodysplasia related changes ($n = 89$, 15.2%) and AML with recurrent genetic abnormalities ($n = 70$, 11.9%). Among patients who received treatment, low, intermediate, and high risk disease according to ELN classification were present in 17.9%, 48% and 16.98% patients, respectively (classification was unknown or not available for 16% patients). In group A, results of karyotyping were available for 240 (74.3%) patients, of which 85 (35.4%) were abnormal. Among these, cytogenetic abnormalities according to ELN good, intermediate and high risk categories were present in 11, 38 and 36 patients, respectively. The most commonly detected good risk anomalies included t(8;21) ($n = 6$), t(16;16) ($n = 2$), and inv16 ($n = 5$). The most common high risk abnormalities identified were del(7q) (n = 10), monosomy 7 (n = 8), del(5q) ($n = 8$), monosomy 5 ($n = 4$), t(9;22) ($n = 4$), and complex karyotypes ($n = 4$). In Group B, a majority of patients had no details of karyotyping (60.8%) or risk stratification (60.3%).

The primary reason for non-initiation of treatment was 'unspecified' in 163 (35%) patients. Among the remaining patients, the commonest reasons for not starting treatment were moving to another center (31%), financial constraints (11.3%) and poor performance statusat diagnosis (9.15%) (Fig. 2).

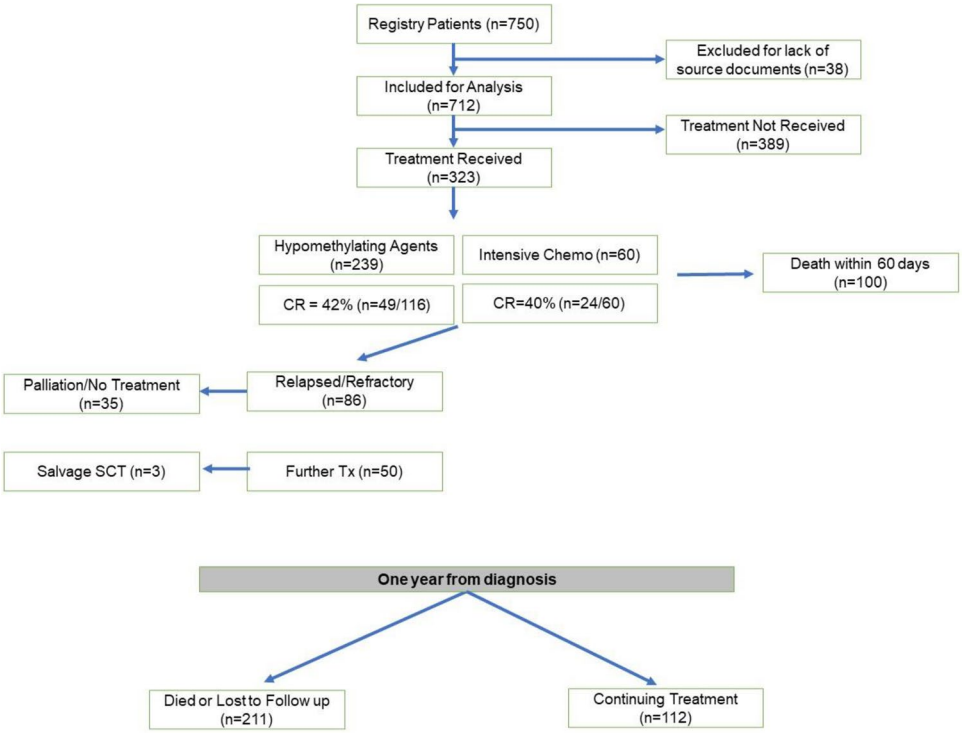

Fig. 1 Consort diagram showing the study population after initial screening. The rates of CR reflect patients who were available for evaluation. Legend: Intensive Chemo included 7/3 induction or its modifications, CR: Complete Remission, SCT: Stem Cell Transplantation, Tx: Treatment

Table 1 Comparison of baseline details among patients who received (Group A) or did not receive (Group B) treatment

Variable	Group A (Mean ± SD / Median (IQR) / N(%)	Group B (Mean ± SD / Median (IQR) / N(%)	*p* value
N (%)	323 (45.3%)	389 (54.6%)	
Age (Years)	62 (59–68)	63 (59–69)	0.146
WBC at diagnosis (cells/mm3)	9640(2800,34,900)	12,150(3500,54,460)	0.037
Hemoglobin (g/dL)	7.90(6.70,9.10)	8(6.70,9.30)	
Platelets (cells/mm3)	50,500(26,000,100,000)	46,000(23,000,89,000)	
Albumin (g/dL)	3.50(3.10,3.90)	3.49(3.10,3.90)	0.516
Creatinine (mg/dL)	0.90(0.70,1.20)	0.90(0.71,1.20)	0.317
WHO Classification	**N (%)**	**N (%)**	
AML-NOS	147 (45.5)	220 (56.7)	
Recurrent Genetic Abnormalities	53 (16.4)	17 (4.3)	
AML-MRC	43 (13.3)	46 (11.8)	
Not Applicable/Unspecified	60 (18.6%)	67 (17.3)	
ELN Risk Stratification			
Low	57 (17.9)	33 (9)	
Intermediate	154 (48.4)	66 (18)	
High	54 (17)	45 (12.4)	
Unknown	53 (16.7)	219 (60.3)	

Legend: *SD* Standard Deviation, *IQR* Interquartile Range, *WBC* White Blood Cell, *WHO* World Health Organization, *AML-NOS* Acute Myeloid Leukemia-Not Otherwise Specified, *AML-MRC* Acute Myeloid Leukemia with Myelodysplasia-Related Changes, *ELN* European Leukemia Net

Initial therapy, complications, and responses

First-line therapy comprised of HMAs in 239 (73.9%) and '7 + 3' induction or its modifications in 60 (18%) patients. In the HMA group, Azacytidine was used in 184 (76.9%) and Decitabine in 55 (23.01%) patients. The remaining minority (7.4%) received alternate intensive or low dose regimens. Seventy nine patients (24%) received targeted oral agents, both as part of first line and subsequent therapy. Most patients received the same in combination with

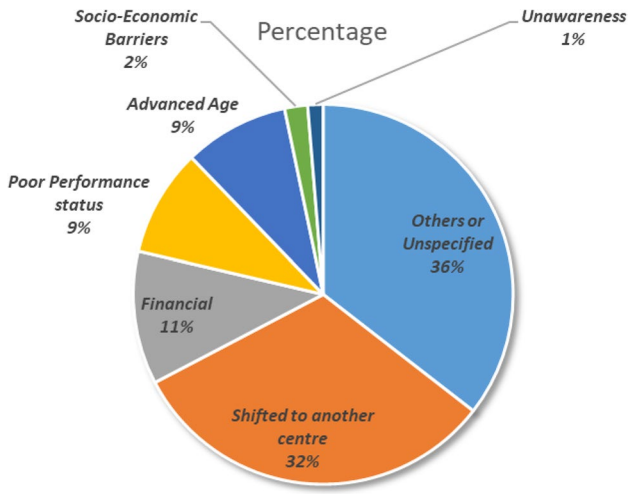

Fig. 2 Distribution of commonest reasons for not initiating treatment among patients in Group B

HMAs ($n=70$, 88%), of which Venetoclax was the most commonly used agent ($n=66$).

After initiation of therapy, 93 patients (31%) encountered infectious complications, and 38 (13.2%) required ICU admission for more than 24 h. Among those receiving IC, a positive blood culture was identified in 33 (55%) patients, of which 12 (32%) isolates were gram negative bacilli and 16 (43%) were mixed infections. Among all the isolates, 16 (50%) were multi drug resistant, including Vancomycin-resistant Enterococci (VRE), Extended-Spectrum Beta-Lactamase (ESBL), and Carbapenem-Resistant Organisms (CRO). In the HMA group, a total of 8 patients had positive blood cultures, all of which isolated gram negative bacilli.Invasive fungal infections (IFIs)were diagnosed in 93 (28.7%) patients, of whicha majority were classified as possible (59.14%)or probable (32.2%)and only 8 (8.6%) were microbiologically proven.

Following induction, complete remission was documented in 24 (39%) patients receiving IC. In the HMA group, 49 (42%) out of 116 evaluable patients achieved CR and 65 (56%) had persistent disease. Response evaluation was not available in 142 patients due to early mortality or loss to follow up. The median time to documentation of CR with HMAs was 86 days (IQR, 36–114). Cumulatively, 23 patients required a second cycle of induction, of which only 5 (21%) received intensive chemotherapy. A total of 100 (31%) patients died within the first 60 days of starting treatment, with the commonest causes being progressive disease (47%) and infections (30%). Among patients who died within 60 days, a majority ($n=80$, 80%) had received HMAs.

Further treatment and follow up

The median duration of follow-up was 176 days (IQR, 43–406). After starting therapy, 116 (37%) patients were lost from follow up and no survival data was available. A majority of patients in Group A discontinued treatment ($n=228$, 76%), with the commonest reasons being movement to another center (35.5%), poor performance status (16.1%) and financial challenges (15.2%).

During the follow up period, 86 (26.7%) patients had relapsed ($n=65$, 75.6%) or refractory ($n=21$, 24%) disease. Fifty patients (58%) from this subgroup received further salvage treatment, of which 23 (46%) received HMAs and others received unspecified low dose chemotherapy or palliative care. Only three patients (3.4%) with relapsed/refractory disease underwent an allogeneic stem cell transplant (AlloSCT).

Survival outcomes

The median overall survival in Group A was 186 days (95% CI, 137–234). At the one year landmark, 211 (65%) patients had died, of which 164 (77%) had available records detailing last clinical assessment. The commonest cause of death was progressive disease, noted in 96 (58%) patients, followed by infectious complications in 34 (20%). Patients who died had a higher median age (63 vs 60 years, $p=0.027$) and baseline WBC counts (11000 vs 4840/mm3, $p=0.006$). No other significant differences were observed among the groups (Table 2). Figure 3 shows Kaplan Meier curve for survival in the entire cohort receiving treatment. Overall survival was significantly lower for patients older than 60 years compared to younger patients (median, 129 vs 286 days, $p<0.001$). When compared by ELN risk groups, a progressive decrease in median OS was noted with increasing risk group (309, 190 and 176 days, respectively) but the difference was not statistically significant ($p=0.065$). Kaplan Meier curves for overall survival classified by age and risk groups are depicted in Figs. 4a and 4b, respectively.

Discussion

We present the largest study of older patients with AML from India, using multicenter collaborative data from the Hematology Cancer Consortium. Notable findings include high rates of non-initiation of treatment and significant underutilization of intensive chemotherapy and stem cell transplantation. We also observe frequent treatment discontinuation and significantly high mortality at both 60 days and one year from diagnosis. These suboptimal outcomes are comparable to published studies with much older populations and reflect the dual challenges of poor disease biology

Table 2 Comparison of baseline characteristics among survivors and non-survivors among patients who underwent treatment in Group A. Details of gender, co-morbidities and infections were missing in 1, 3 and 9 patients respectively

	Alive (Mean ± SD / Median (IQR) / N(%)	Dead (Mean ± SD / Median (IQR) / N(%)	*p*-value
Total Number	69	253	
Age (Years)	60 (58–66)	63 (59–69)	.027
WBC Count (cells/mm3)	4840 (2050–19150)	11,000 (3055–40000)	.006
Albumin (g/L)	3.6 (3.2–4.0)	3.5 (3.0–3.8)	.015
Creatinine (mg/dl)	0.8 (0.6–1.16)	0.9 (0.71–1.20)	.007
Gender			
Male	35(50.72)	156(61.66)	0.101
Female	34(49.28)	97(38.34)	
Total	69(100.0)	253 (100.0)	
Co-morbidities			
No	30(43.48)	92(36.65)	0.301
Yes	39(56.52)	159(63.35)	
Total	69(100.0)	251(100.0)	
Infection requiring antibiotics at diagnosis			
Yes	26(37.68)	85(34.69)	0.647
No	43(62.32)	160(65.31)	
Total	69(100.0)	245(100.0)	

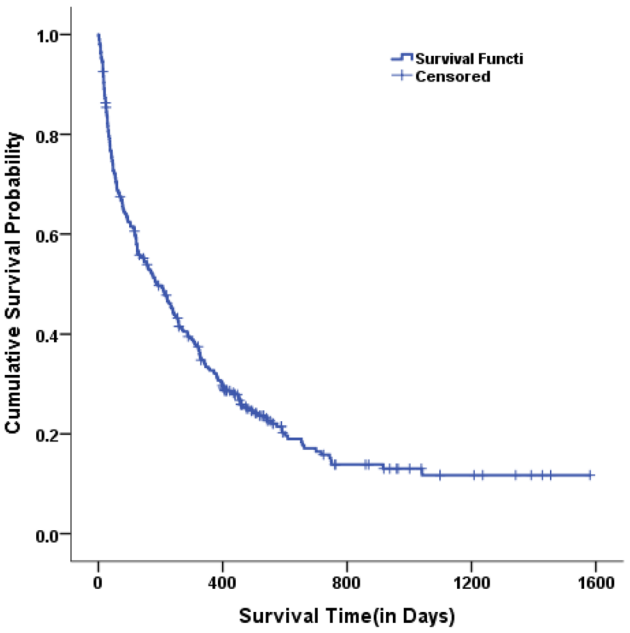

Fig. 3 Kaplan–Meier curve showing overall survival of patients initiating treatment at one year from diagnosis ($n = 323$)

and socioeconomic factors that hinder effective treatment of AML in resource constrained settings.

Globally, a significant proportion of older patients with AML do not receive treatment with curative intent, even in settings with universal healthcare coverage.[15]In an analysis of SEER (Surveillance, Epidemiology, and End Results) data including 14,000 patients with a median age of 78 years, approximately 50% of the entire cohort and 82% of those aged above 80 years did not receive any treatment. [16]We observed similar rates of undertreatment in a much younger cohort, with the utilization of intensive chemotherapy being even lower. Only 18% of patients in our study received intensive induction, compared to 81% of patients aged 60–69 years and 41% of those aged 70–79 years based on U.S. data. [17]These findings likely reflect concerns about treatment-related mortality and physiologic frailty in Indian patients. Even with low utilization of IC, mortality at 60 days was significantly higher compared to older patients from European registry data (31 vs 13%) [18] Indeed, the mortality rates in our study are similar to those observed at median ages of 70–80 years in Western cohorts [19–21].

Infections, especially drug resistant gram negative and invasive fungal infections continue to be the next most important contributor to treatment related mortality in AML and contributed to 30% of early deaths in our cohort. [20, 22, 23] Microbiologic evidence of infection was obtained in 30% of patients, with nearly half the isolates being multi drug resistant. MDR infections are increasingly being implicated as the cause of death in Indian patients with AML, at a frequency ranging from 20–40% in various studies including patients with median age ranging from 23 to 40 years. [8, 24] This is an emerging and concerning issue and warrants urgent evaluation of antibiotic drug policies for patients with neutropenic fever.

We observed a higher incidence of IFIs compared to published data from the West where the incidence is typically around 10%. [25] This finding is in keeping with other large

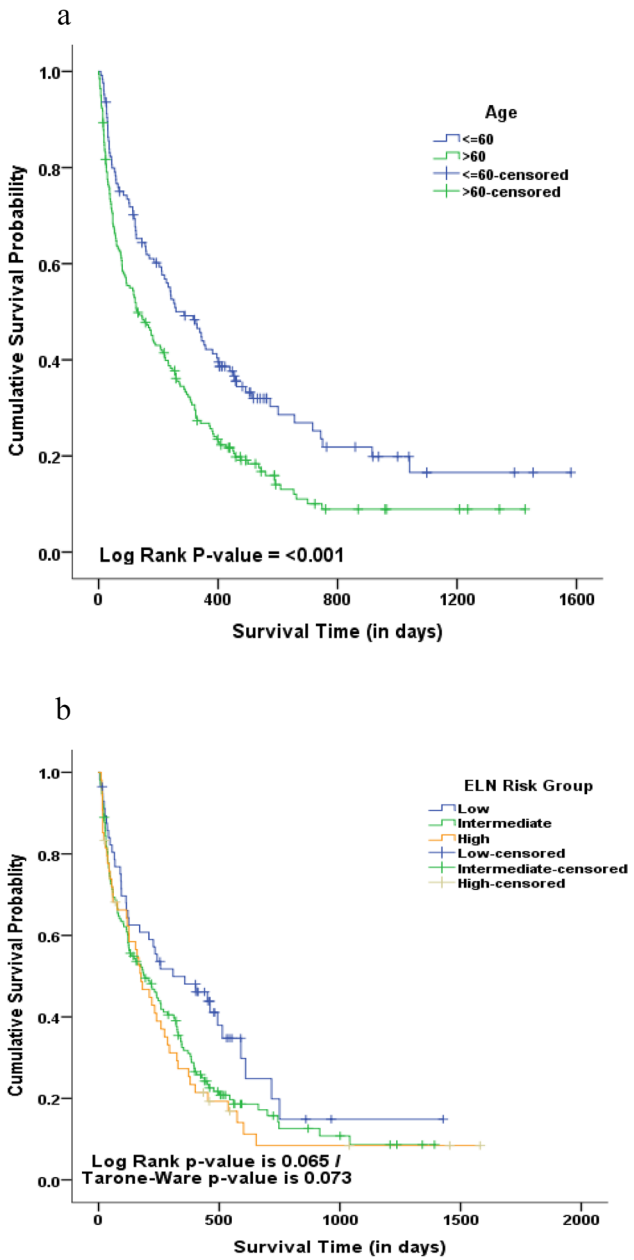

Fig. 4 **a**: Comparison of overall survival in patients ≤ 60 or more than 60 years of age. Legend: Median one year survival in patients younger than 60 years of age was significantly higher (286 vs 129 days, $p < .001$). **b**: Fig. 4b: Comparison of overall survival based on ELN risk stratification. Median OS for low, intermediate and high risk groups was 309, 190 and 176 days, respectively

Indian datasets and may indicate a higher baseline risk of IFIs due to frailty or delayed presentation. [26, 27].

Financial barriers emerged as a significant modifiable factor for non-initiation of therapy in our study, similar to findings by Philip et al. [8] Financial toxicity after a diagnosis of cancer is very prevalent in India, and is expected to be higher for AML due to high costs of treatment. [28] Public funding for cancer in India is heterogeneous, and many programs are either restricted to select institutions or insufficient to cover the cost of care for AML or stem cell transplantation. A population-level costing exercise similar to Sweden may allow identification of public costs of treating AML based on age, disease subtype, and expected survival, can help in better rates of treatment. [29].

Only twelve patients in our study underwent allogeneic stem cell transplantation (9 in initial remission and 3 after relapse). AlloSCT, particularly with reduced intensity conditioning prolongs overall survival compared to conventional therapy in patients older than 60 years of age, with one year OS of approximately 60%. [30, 31] Although outcomes with SCT for AML are progressively improving in India, caveats for physiologic frailty must factor in the decision for the same [32, 33].

We compared our findings with other large registries including older patients with AML. (Table 3)Significantly, we observe similar survival outcomes despite a much younger population. These results highlight the importance of evaluating HMA and Venetoclax based regimens, possibly combined with stem cell transplants as the initial choice for Indian patients aged 55 years and older. [34, 35] Considering the low median age of our population compared to published data, we compared outcomes with select studies evaluating patients at an intermediate age range of 59 to 75 years (Table 4). Our findings of similar or poorer survival outcomes compared to even younger populations further emphasize the concerningly low survival rates in our study cohort.

Suboptimal outcomes with AML in India appear to result from several factors, including higher physiologic frailty, perception of oncologists regarding treatment tolerance, high rates of MDR infections, availability of treatment facilities and competing needs from other cancers.

These findings indicate greater physiologic frailty in Indian patients which is evident at a much younger age. While earlier studies showed higher rates of CRin older patients receiving intensive chemotherapy (IC), we did not observe the same in our data [40, 41, 42]. Along with emerging data on high rates of CR with Venetoclax based combinations, these findings make it increasingly difficult to justify intensive chemotherapy for potentially frail patients. Objective assessment of frailty independent of chronological age is vital to balance treatment efficacy and toxicity and is aided by several composite tools such as the comprehensive geriatric assessment (CGA), short physical performance batter (SPPB) and mini mental state examination (MMSE) in older patients with AML [43, 44]. It is essential to validate these tools in the Indian context to guide treatment decisions.

Additionally, formal assessment of frailty, evaluation of Venetoclax and HMAs in reducing treatment related mortality in induction, novel consolidation strategies

Table 3 Salient comparison with other registries describing outcomes in older patients with AML

	Swedish AML Registry	SEER Database	Danish Registry	European Registries: DATAML, PETHEMA and SAL	This Study (HCC-InWARD Registry)
Year	2009	2013	2020	2022	2022
N	2767	5415	1725	2272	718
Age	Median 72 years	≥65 years	≥71 years	Median 75 years	≥55 years
Proportion of IC	62%	N/A	14.9%	52.7%	18%
Early Mortality (Days)	19% (30 days)	N/A	16–54% across various age groups	19.4% (60 days)	31% (60 days)
Overall Survival	Median 196 days; 500 days for those receiving intensive chemotherapy	20% relative survival at 12 months for 65–74 year ages	One year survival ~ 20% between 2013–2016	10.5 months with IC, 9.2 months with HMA	35% at 12 months, Median 186 days
Patients undergoing Transplant	N/A	N/A		3.3%	3.3%
Others		Improved Relative survival compared from 1977 to 2006 for 65–74 year olds, not for those > 75			75% patients discontinued treatment, survival better for those < 60 years of age

SEER Surveillance, Epidemiology, and End Results, *PETHEMA* Programa Español de Tratamientos en Hematología, *SAL* Study Alliance Leukemia, *N/A* Not Applicable, *IC* Intensive Chemotherapy

Table 4 Comparison of Outcomes in Intermediate-Aged AML Patients (55–74 years) from Literature. The present study observes a lower survival despite a lower age threshold

Study	Year	Age Group	N	Survival
Applebaum et al. [36]	2006	56 to 65 years	246	Median OS 9.0 (8.1–10.2) months
Oral et al. [37]	2012	65–69 years	512	Median OS 9 months
		70–74 years	627	Median OS 8 months
Abuelgasim et al. [38]	2020	40–59	9253	Relative Survival at 1 year: 66.3% (65.4–67.3))
		60 to 74 years	9798	Relative Survival at 1 year: 47.8% (46.8–48.8)
Zeidan et al. [39]	2020	> 60 years	288	Median OS 7.1 months for entire study, HR for death for 60–69 vs 70–74 was 1.29 (1.11–1.50)
Present Study	2023	> 55 years	712	Median OS: 6.2 months (IQR, 4.5 months to 7.8 months), 35% patients alive at one year

and optimization of use of alloSCT may further help in improving outcomes in this population.

The primary strength of our study is based on the utilization of multicenter data, offering a varied perspective from government, academic and private facilities. The ongoing registry has been updated in 2022 to capture detailed data on targeted molecular agents the same and is expected to provide greater insights in the future.

Our study provides the first large scale overview of treatment patterns and outcomes of older patients with AML from India and indicates a higher risk of mortality, possibly due to younger onset of physiologic frailty. These findings set the stage for future research focusing on assessment of molecular disparities contributing to outcomes and frailty, as well as prospective evaluation of novel targeted agents in this high risk population.

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Author contribution SS and SL wrote the initial proposal and concept outline. HJ, SK, MS and VM developed and reviewed the CRF. PS, OP and BU performed data verification and statistical analysis. SS and SL wrote the paper. MS and VM oversaw overall direction and planning. HJ, AR, LN, RA, NA, PDS, PB, MJJ, KM, MP, LKA, PG, CCP, DD,

VS, PM, JPK, VR, SCB, BR, SM, UB, BB, AA, RK, DB contributed to data entry and reviewed the final manuscript.

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Data availability Data is stored centrally with Clinical Data Management Centre (CDMC), Department of Biostatistics, Christian Medical College, Vellore and is available on request.

Declarations

Ethical approval Ethical Committee and Institutional Research Board clearance was obtained by each institution before participation in the study in compliance with established guidelines. Documents for the same from each institution are available with the registry.

Competing interests The authors declare no competing interests.

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