Outcomes in adolescent and young adult acute lymphoblastic leukaemia: a report from the Indian Acute Leukaemia Research Database (INwARD) of the Hematology Cancer Consortium (HCC)

Adolescent and young adult (AYA) patients with acute lymphoblastic leukaemia (ALL) have inferior survival when compared to children. The causes are multiple and include bad biology, differences in treatment approaches, and other complex social, economic and psychological factors that affect therapy adherence.[1] Intensive 'paediatric' regimens improve outcomes, but these come with the cost of higher toxicity, which may even negate these benefit of reduced relapse.[2–5] To understand the *real-world* data from India, we analysed the outcomes of AYA ALL (aged 15–29 years, treated between 2012 and 2017) from a retrospective database maintained by the Hematology Cancer Consortium (HCC). Baseline data of all patients (including those who were not treated) diagnosed within the period stipulated by a particular centre were captured, including reasons for not availing treatment. Survival outcomes were estimated for treated patients (censored on 31 July 2019). For this analysis, 'high risk' was defined based on white blood cell count (WBC) at diagnosis (B cell >30 × 10^9/l, T cell >100 × 10^9/l). Protocols such as Multicentre protocol 841 (MCP-841), Berlin-Frankfurt-Münster 95 (BFM-95), BFM-90, and Children's Oncology Group (COG) were considered 'paediatric type', whereas German Multicentre ALL (GMALL), hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), and UKALL were considered 'adult type'. Minimal residual disease (MRD) >0·01% (when assessed by flow cytometry) was considered positive.

Of the 1383 patients registered, 1141(82·5%) underwent treatment (Supplementary Table S1 and S2, baseline characteristics), and 242 did not start treatment (Fig 1). The inability to afford treatment was the commonest cause for not initiating treatment (105/1383, 7·6%). There were no

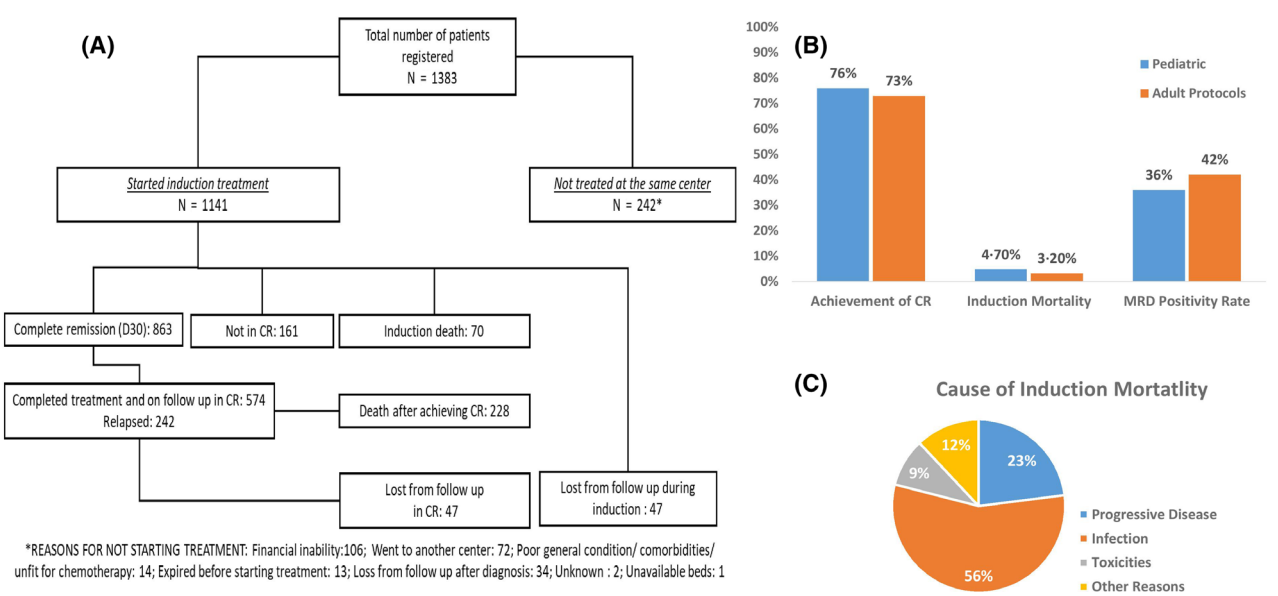

Fig 1. Flowchart depicting the outcomes of patients who were included in the registry. Of the 1383 patients, only 1141 started therapy (induction) and 863 (76%) achieved complete remission (CR). At last follow-up, 574 were in CR and on follow-up. A total of 336/1383 (24%) patients either did not start therapy (N = 242), or abandoned therapy after starting induction (N = 94) (**A**). (**B**) Comparison of induction outcomes between those treated with 'paediatric' and 'adult' protocols. There were no differences in terms of achievement of CR (76% vs. 73%, P = 0·509), induction mortality (4·7% vs. 3·2%, P = 0·842), or minimal residual disease (MRD) positivity rate (36% vs. 42%, P = 0·382). (**C**) The commonest cause of induction mortality was infection (56%) followed by progressive disease (23%).]

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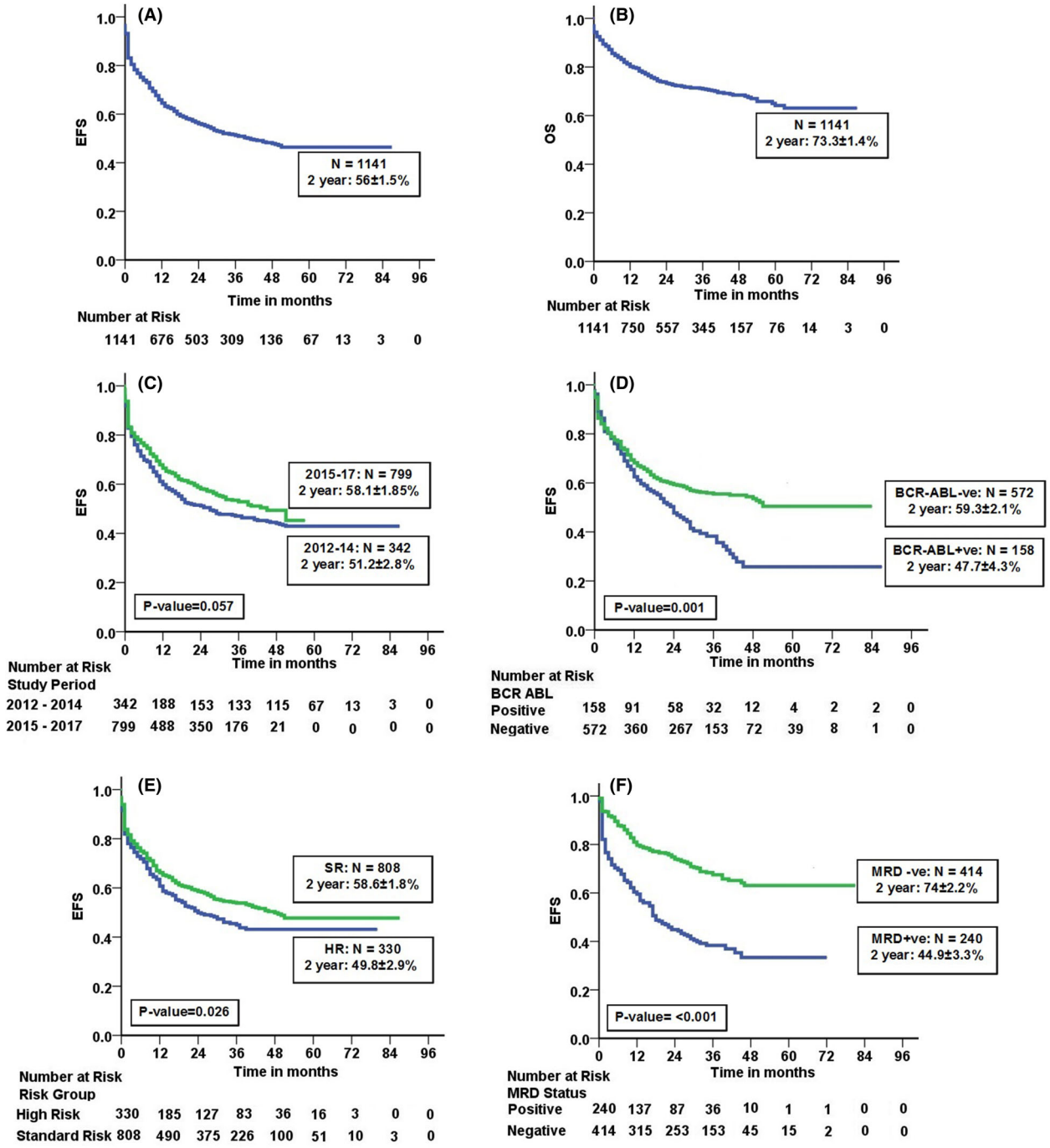

Fig 2. Kaplan–Meier estimates of event-free (EFS) and overall survival (OS). The 2-year EFS (**A**) and OS (**B**) of patients with AYA ALL ($N = 1141$) was 56% and 73% respectively. Kaplan–Meier curves depicting the EFS comparison between baseline factors: study period early (blue) vs. later (green) (2-year EFS 51% vs. 58%, $P = 0{\cdot}057$) (**C**), *BCR-ABL* negative (green) vs. positive (blue) (2-year EFS 59% vs. 48%, $P = 0{\cdot}001$) (**D**), standard risk (green) vs. high risk (blue) (2-year EFS 59% vs. 50%, $P = 0{\cdot}026$) (**E**), and MRD negative (green) vs. positive (blue) at the end of induction (2-year EFS 74% vs. 45%, $P < 0{\cdot}001$) (**F**). *P* values show comparison using the log-rank test.

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differences in the baseline variables between treated and untreated patients (Supplementary Table S1). The BFM protocol (BFM-90, -95 or -2000) was the commonest regimen used ($n = 846$, 74%). Those treated with paediatric (1002, 87·8%) protocols had a lower median age (20 vs. 23 years, $P = 0{\cdot}001$) when compared to those treated with adult protocols (Supplementary Table S2). After induction, 76% achieved complete remission (CR), and MRD was positive in

240/654 (37%). A total of 70 patients died during induction, most commonly due to infections (Fig 1C). Induction outcomes were similar between the paediatric and adult protocols (Fig 1B). After starting induction, 94 additional patients abandoned therapy (47 during induction therapy and 47 during subsequent follow-up after achieving CR).

After a median follow-up of 23 months [95% confidence interval (CI) 6–38] (32·2 months by reverse-censoring method), 242 (28%) patients had relapsed [median (interquartile range, IQR) time to relapse: 11 (7, 21) months] and 298 had died [causes of death: progressive disease (151, 51%), infection (77, 26%), toxicity other than infection (22, 7%), and unknown causes (48, 16%)]. The estimated 2-year event-free (EFS), relapse-free (RFS) and overall survival (OS) were 56%, 75% and 73% respectively (Fig 2A, B). On univariate analysis, inferior EFS (Supplementary Table S2) was associated with high-risk disease, breakpoint cluster region-Abelson (*BCR-ABL*)-positive status and MRD positivity (Fig 2C–F), and inferior OS with earlier period of diagnosis, use of adult-type protocols [hazard ratio (HR) 1·72, 95% CI 1·29–2·29] and MRD positivity. On multivariate analysis, inferior EFS was associated with an earlier period of diagnosis, MRD positive disease and *BCR-ABL*-positive status (Supplementary Table S3), and inferior OS with earlier period of diagnosis, use of adult-type protocols, and MRD-positive status (Fig 2). The presence of *BCR-ABL* (either by reverse transcriptase-polymerase chain reaction or by fluorescence *in situ* hybridisation at diagnosis) was tested in 730 patients and was found to be positive in 158 (22%). The 2-year EFS among *BCR-ABL*-positive and -negative patients was 48% and 59% respectively ($P = 0{\cdot}001$).

Our dataset included patients from across the socioeconomic strata with variable levels of financial support (government, insurance, self-pay). Nearly a quarter (336/1383, 24%) of the patients either did not start treatment ($N = 242$) or abandoned therapy after starting ($N = 94$), which is one of the major challenges when treating AYA patients in resource-challenged situations. The other major challenge in using more intense therapies in young adults is the increased mortality, which has been noted in earlier Indian studies.[4,6] However, this was not was not seen in the present data and the majority were treated with intensive paediatric-type protocols without excess treatment-associated mortality. The 2-year EFS in the present study (56%) is lower than that reported from clinical trials of AYA ALL (survival >70%) (Supplementary Table S4). However, it is comparable to 'real-world' data (60–65% EFS at 3–5 years) reported from USA centres.[7]

Based on WBC count at diagnosis, risk grouping was predictive of EFS on univariate analysis, but was not predictive on multivariate analysis. MRD assessment was available for 654 patients in our present study and was positive in 36%, which is similar to the rate reported in other studies.[3,8] In our present study, the MRD assessment was not used to change therapy. Many recent studies in the AYA age group have shown that the persistence of post-induction MRD reduces EFS by 15–40%.[3,8–10] (Supplementary Table S4).

Treatment non-adherence and abandonment are well-recognised challenges when treating AYA patients.[11] Although treatment costs were identified in a proportion of patients as the reason for not initiating therapy, other reasons need to be sought out and addressed. Most patients need to travel to bigger cities and stay for there for treatment, which leads to added costs, loss of livelihood in the patient or caregiver, and other psychological factors may also contribute to this problem. The present analysis is limited by the variations in treatment protocols, lack of baseline cytogenetic data, and relatively short follow-up. Important data on symptom duration and distance from the centre were not available. Nevertheless, this is one of the largest reports on the outcomes of AYA ALL and provides a strong foundation for planning future studies.

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Author Contributions

Prasanth Ganesan, Vikram Mathews and Manju Sengar, performed research, designed the study, analysed the data and wrote the paper; Hasmukh Jain, performed research, analysed the data and wrote the paper; Bhausaheb Bagal, Papagudi G. Subramanian, Biju George, Anu Korula, Nikita Mehra, Jayachandran P. Kalaiyarasi, Dinesh Bhurani, Narendra Agrawal, Rayaz Ahmed, Smita Kayal, Jina Bhattacharyya, Uday Yanamandra, Chepsy C. Philip and M. Joseph John performed research and analysed the data; Ambily Nadaraj, Omprakash Karunamurthy and Jeyaseelan Lakshmanan, performed statistical analysis of the data.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of all registered patients (N = 1383)

Table S2. Factors affecting survival (compared using log-rank analysis) in adolescent and young adult acute lymphoblastic leukaemia

Table S3. Cox proportional hazard regression model for event-free (EFS) and overall survival (OS)

Table S4. Comparison of data from studies of adolescent and young adult (AYA) patients treated for acute lymphoblastic leukaemia (ALL)

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