Indian J Hematol Blood Transfus (Apr-June 2019) 35(2):248–254
https://doi.org/10.1007/s12288-018-1023-0

ORIGINAL ARTICLE

# Outcomes of Intensive Treatment of Adult Acute Myeloid Leukemia Patients: A Retrospective Study From a Single Centre

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Received: 21 June 2018 / Accepted: 25 September 2018 / Published online: 1 October 2018


**Abstract** Background: Acute Myeloid Leukemia (AML) is a very aggressive cancer with difficult treatment and poor outcomes. The treatment of these patients is quite challenging due to various reasons including the need for extensive supportive care, and high cost of therapy. Reports on outcomes from India are few. Methods: We analyzed 93 adult patients (≥ 18 years) with AML who were treated with curative intent between 2007 and 2014. Patients received daunorubicin at dose of 60–90 mg/m$^2$ and cytarabine 100 mg/m$^2$ during induction and consolidation with 3 courses of high dose cytarabine (1.5–3 g/m$^2$per dose for 6 doses per cycle). Only 4 patients underwent consolidation allogenic stem cell transplantation in first remission (CR1). Results: The median age was 37 (18–66) years; males: 52%. Conventional cytogenetics (N = 63) showed 23% (N = 15), 56% (N = 35), 27% (N = 13) in good, intermediate risk and poor risk category respectively. *FLT3–ITD* was positive in 12/33 (36%) and *NPM* mutation in 7/23 (30%). Daunorubicin dose was 60 mg/m$^2$ in 75% (N = 70) and 90 mg/m$^2$ in 25% (N = 23) patients. Induction mortality was 17% (16/93) [60 mg/m$^2$:19% (13/70), and 90 mg/m$^2$:13% (3/23); $p = 0.39$)]. Complete remission was achieved by 60% (56/93) [60 mg/m$^2$:53% (37/70), and 90 mg/m$^2$:83% (19/23); $p = 0.09$)]. The median overall survival was 9.2 months and the actuarial survival at 2 years was 30%. By univariate analysis, *FLT3-ITD* positivity, white cell counts higher than 100,000/mm$^3$ at presentation, and use of lower dose of daunorubicin in induction were associated with poorer outcomes. Conclusions: Outcomes in adult AML are generally poor. Many patients with high risk disease don't receive allogenic transplantation in CR1. Increased availability of allogenic stem cell transplantation may help to improve outcomes.

**Keywords** Acute myeloid leukemia · India · Daunorubicin · Outcomes · Risk stratification · Mortality

## Introduction

Acute Myeloid Leukemia (AML) in adults is an aggressive hematological malignancy with poor outcomes. Induction therapy with a combination of anthracycline and cytarabine, first used almost 4 decades back continues to remain the standard therapy and produces remission in about 60–70% patients [1]. Post-remission therapy consists of 2–4 cycles of high dose cytarabine in low risk disease, while allogenic transplant is considered the best option for patients with intermediate and high risk AML [2]. Survival in young adult patients with AML has improved due to better supportive treatment and risk stratified treatment approach [3, 4]. Multiple challenges are posed when treating AML in Indian conditions. The high cost of treatment due to requirement for extensive supportive care, limited availability of stem cell transplant facilities and recent surge in multi-drug resistant infections are some of these [5, 6]. Very few centers in India routinely treat patients with AML and even in these centers, only a proportion of patients who present with the disease actually end up taking therapy [6]. We present the outcomes of therapy of AML from a South Indian center catering towards low and middle income patients. This study represents only the select population of patients who were

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indexed in our hospital and excludes many patients who presented to the outpatient and did not pursue further investigations or therapy at our center due to various reasons.

## Methods

### Patients

Between January 2007 and December 2014, 103 patients with AML in the age group of $\geq$ 18 years were treated. These were patients who were indexed and planned for therapy at our center. There were patients who visited our out-patient and did not undergo further evaluation or treatment at our centre. They were not indexed in the hospital registry and the data and number of these patients was not available. Of these 103, 93 patients, who were treated with curative intent and given induction therapy with a combination of daunorubicin and cytarabine were included for analysis. The other 10 patients received only palliative treatment/decitabine/low dose cytarabine. Patients with acute promyelocytic leukemia were excluded from this analysis. The clinical and laboratory information and details of subsequent treatment and outcome were obtained from patient records. Diagnosis of AML was established by demonstration of $>$ 20% myeloblasts on bone marrow aspirate by combined morphology, cytochemistry and flowcytometry [7]. Conventional cytogenetic analysis was attempted in most patients. Patients treated after 2013 had analysis of Fms-like tyrosine kinase gene internal tandem duplication (*FLT3*-ITD) and nucleophosmin 1 (*NPM1)* gene mutation status assessed by RT-PCR. Patients were categorized as good, intermediate and poor risk on the basis of cytogenetic results.

### Treatment Details

Induction chemotherapy included cytarabine (100 mg/m$^2$/day over 7 days as continuous infusion) and daunorubicin (60–90 mg/m$^2$/day over 2 h on days 1–3). The dose of daunorubicin was 60 mg/m$^2$ till 2012—subsequently it was modified to 90 mg/m$^2$ for patients who were young, fit and those who presented without baseline infections. This was based on the results of a study which showed superior outcomes with Daunorubicin 90 mg/m$^2$ over 45 mg/m$^2$ [8]. Less intensive treatments like 2 + 5 (DNR 60 mg/m$^2$ for 2 days and cytarabine 100 mg/m$^2$ for 5 days), 3 + 5 (DNR 45 or 60 mg/m$^2$ for 3 days and cytarabine 100 mg/m$^2$ for 5 days) were given to few patients (N = 3) who had multiple comorbidities or in those who presented with sepsis. Patients achieving complete remission (CR) post-induction therapy were given consolidation therapy with either three cycles of high-dose cytarabine (HIDAC, 2007–2011, 18 g/m$^2$ divided over 3 days) or three cycles of intermediate-dose cytarabine (IDAC, 2012–2014, 9 g/m$^2$ over 3 days). The dose of cytarabine was reduced based on our perception of increased toxicity at that time with the higher dose and also data which had emerged that a lower dose would be equally effective [9–11]. Only 4 patients received allogenic stem cell transplantation as consolidation for intermediate or high risk disease.

### Supportive Care

All patients received antifungal prophylaxis with fluconazole (2007–2011) or voriconazole (after 2012), and anti-herpes prophylaxis with acyclovir. Routine anti-bacterial prophylaxis was not used. At the onset of fever, after evaluation, patients were started empirically on broad spectrum antibiotics (cefoperazone/sulbactam) and amikacin. Antibiotics were modified depending upon the blood culture reports or clinical response. Teicoplanin was added for suspected gram positive infections (mucositis, severe pneumonia, skin and soft tissue infections). Amphotericin-B was the preferred anti-fungal which was used empirically for persistent fever or based on clinical and radiological clues. Evaluation included history, physical examination, chest X-ray, blood culture (peripheral and central line), urine analysis and appropriate cultures. Additional blood cultures were also taken during changes in fever pattern and when the patient showed deterioration. High-resolution computed tomography scan of chest was done in patients with persistent fever, having pulmonary infiltrate on chest X-ray and in those suspected to have fungal infection (Fig. 1).

### Outcome Variables and Analysis

Complete response (CR) was defined as: $<$ 5% of blasts in bone marrow, no leukemic blasts in peripheral blood, and recovery of peripheral blood values to neutrophil counts of at least 1000/μL and platelet counts of at least 100 000/μL, and no evidence of extra medullary leukemia. Refractory leukemia was defined as persisting blasts in blood and/or bone marrow in patients after two induction chemotherapies. Induction death was defined as death occurring within the first month following induction therapy (first or second induction). Relapse was defined as the presence of at least one of the following: recurrence of more than 5% of leukemic cells in bone marrow or any leukemic cells in peripheral blood or extra medullary sites. Overall survival (OS) was calculated as the time from the day of diagnosis to death or last visit.

Baseline characteristics were reported as descriptive statistics and differences between categorical outcome

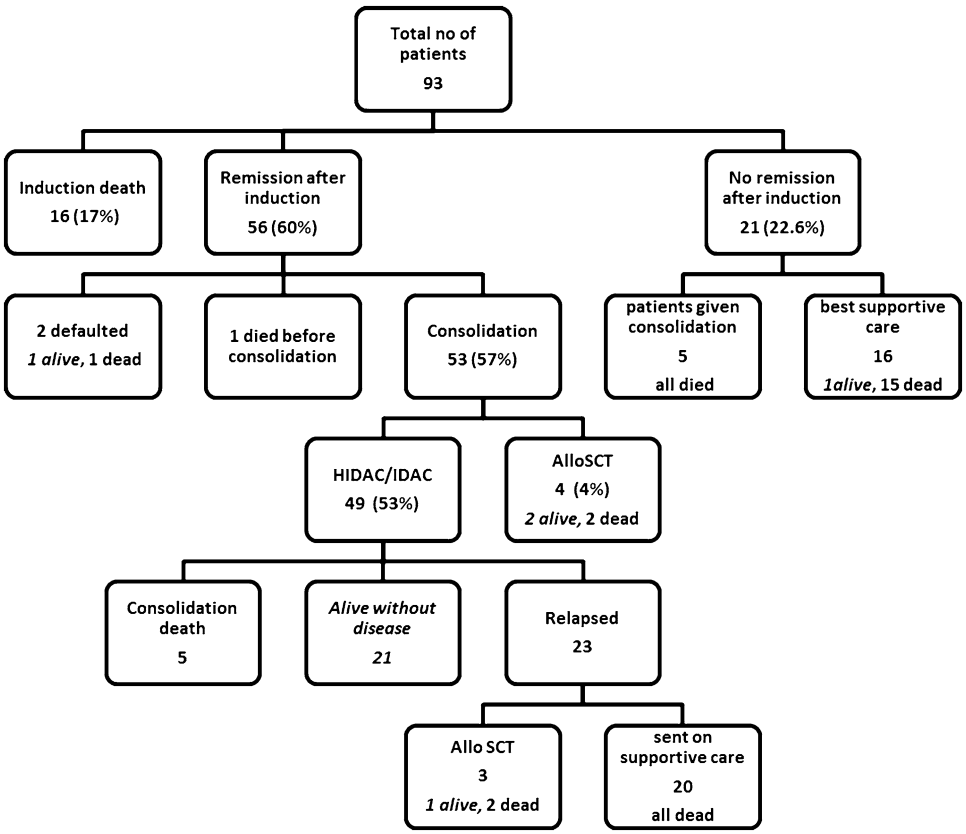


**Fig. 1** Flow chart showing the outcomes of patients included in the retrospective analysis

variables were compared using the Chi square test. Overall survival (OS) was estimated using Kaplan- Meier method and the factors affecting survival were compared using the log-rank test [SPSS version 13.0 (IBM Inc.)].

## Results

Baseline characteristics of the patients are shown in Table 1. The median age was 37 years (19–63) and most (55%) were intermediate risk. Daunorubicin was given at a dose of 60 mg/m$^2$ body surface area in 75% of patients. Among the patients who achieved CR after induction, half (50%) received cytarabine at intermediate doses (9 g/m$^2$). The *FLT3*–ITD mutation and *NPM1* mutation was found in 36% and 30% respectively (Table 1). Only 4 patients received allogenic SCT in CR1.

### Induction Outcomes

Fifty-six patients (60%) attained complete remission (CR) after induction. The complete remission rate was significantly higher with the Daunorubicin 90 mg/m$^2$ [82.6% compared to 52.9% in 60 mg/m$^2$ ($p$ = 0.009)]. Sixteen patients (17%) died during induction (mortality in daunorubicin 60 mg/m$^2$ vs. 90 mg/m$^2$ = 18% vs. 13%; $p$ value 0.399).

### Toxicity During Induction

Major cause of induction mortality was sepsis (14/16); one had intra cranial bleeding and one had cardiac failure. Among the patients who had sepsis, 7 had a focus of pneumonia, 1 had necrotizing fasciitis, 1 had neutropenic colitis and 5 had no proven focus of infection. Culture proven sepsis was seen in 4/14 patients of which 2 had multi-drug resistant (carbapenem resistant) gram negative bacilli, 1 had candida and 1 had methicillin-resistant *Staphylococcus aureus*.

Out of the remaining 77 patients, 75 had febrile neutropenia with identifiable foci in lung [(N = 13, fungal (N = 8) non-fungal (N = 5)], soft tissues [N = 3, fungal (N = 1) and bacterial (N = 2)], and central line [N = 2]. Microbiological identification of the organism was done in 10 patients and included *Eschesrichia coli* (N = 2), *Klebsiella pneumonia* (N = 3), *Pseudomonas aeruginosa* (N = 2), *Acinetobacter baumanii* (N = 1), *enterococcus sp.* (N = 1) and *Staphylococcus aureus* (N = 1). Non-infectious complications included major bleeding (N = 3) and cortical venous thrombosis (N = 1).

**Table 1** Baseline characteristics of patients with AML treated with 3 + 7 (N = 93)

| Characteristics | N (%) |
|---|---|
| Male sex | 48 (52) |
| Median age, years (range) | 37 (19–63) |
| Cytogenetic risk category (N = 63)[a] | |
| Good | 15 (24) |
| Intermediate | 35 (55) |
| Poor | 13 (21) |
| FAB classification | |
| M0 | 1 (1) |
| M1 | 2 (2) |
| M2 | 37 (40) |
| M4 | 18 (19) |
| M5 | 1 (1) |
| M6 | 9 (10) |
| Unclassified | 25 (27) |
| Secondary AML | 4 (4) |
| *FLT3*–ITD (N = 33) | |
| Positive | 12 (36) |
| Negative | 21 (64) |
| *NPM1* mutation (N = 23) | |
| Positive | 7 (30) |
| Negative | 16 (70) |
| Daunorubicin dose in induction | |
| 60 mg/m$^2$ × 3 days | 70 (75) |
| 90 mg/m$^2$ × 3 days | 23 (25) |
| Cytarabine dose in consolidation (N = 52)[b] | |
| 1.5 g/m$^2$ × 6 doses | 26 (50) |
| 3 g/m$^2$ × 6 doses | 26 (50) |

[a]The rest of the patients did not have baseline cytogenetic data because of either non-available sample (N = 22) or no metaphases on the smear (N = 8)

[b]Data only for those patients who underwent consolidation therapy and represents the dose given in each cycle of consolidation

## Consolidation Therapy

High dose/intermediate dose cytosine was given as consolidation in 49 patients, of which 35 patients had febrile neutropenia, 2 had a major CNS bleeding and 1 had cerebellar toxicity. There were 5 deaths during consolidation out of 49 patients who received high dose/intermediate dose cytosine as consolidation. All the 5 patients died due to sepsis of which only one had microbiologically documented infection (gram negative bacilli).

## Survival Analysis

After a median follow up of 9 months (range: 1–86 months, follow-up in live patients: 29 months), the median OS was 9.2 months with estimated 2-year OS of 30% (95% CI 6.7–13 months) (Fig. 2). On univariate analysis (Table 2), WBC counts higher than 100,000/cmm at presentation, *FLT3*-ITD positivity and lower dose of daunorubicin (60 vs 90) were associated with inferior OS. The 2-year overall survival in patients who received 90 mg/m$^2$ daunorubicin in induction was 54.8% compared to 21.6% in those who got 60 mg/m$^2$ ($p$ = 0.018).The dose of cytarabine in consolidation did not impact on the outcomes. The 2-year overall survival in patients who received 3 g/m$^2$ cytarabine during consolidation was 43.7% compared to 53.2% in patients who received 1.5 g/m$^2$ ($p$ = 0.83) (Fig. 3).

## Discussion

Though AML is one of the commonest hematological cancers among adults, there is paucity of published data from India. Earlier reports had shown that very few patients who present to a tertiary hospital undergo treatment, mainly due to financial constraints [6]. In our analysis, mainly dealing with adult subjects who got intensive therapy, the survival rate was 30% at 2 years. For a period, we had used 90 mg/m$^2$ daunorubicin in induction and in our analysis, we found a better outcome in those patients than those who received 60 mg/m$^2$. It is possible the bias involved in selecting the patients who are young, fit and without baseline infection for a higher dose of daunorubicin would be the reason for better outcomes. A recent phase III trial comparing the daunorubicin dose of 60 mg/m$^2$ and 90 mg/m$^2$ showed that the survival was not

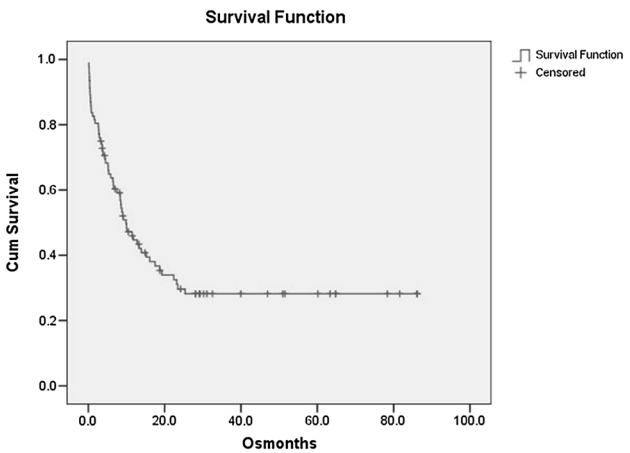


**Fig. 2** Overall survival of the entire study population (N = 93)

**Table 2** Univariate analysis of factors affecting overall survival (OS)

| Factor | Category | OS at 2 years (%) | Median OS (months) | *p* value |
|---|---|---|---|---|
| Age | < 50 years | 32.5 | 10 | 0.416 |
| | ≥ 50 years | 19.4 | 8.4 | |
| Total WBC count | < 100,000/cc | 37.7 | 11.4 | **0.02** |
| | ≥ 100,000/cc | 9.8 | 6.6 | |
| Cytogenetic risk[a] | Good | 66 | NR | 0.108 |
| | Intermediate | 29 | 13.3 | |
| | Poor | 23 | 8.3 | |
| *FLT3*–ITD[b] | Negative | 33.3 | 15.2 | **0.04** |
| | Positive | 16.7 | 4.5 | |
| *NPM1* mutation[b] | Positive | 42.9 | 11.4 | 0.711 |
| | Negative | 23.8 | 9.1 | |
| Daunorubicin dose induction | 90 mg/m$^2$ | 54.8 | NR | **0.018** |
| | 60 mg/m$^2$ | 21.4 | 8.8 | |
| Cytarabine dose consolidation | 1.5 gm/m$^2$ | 53.2 | NR | 0.83 |
| | 3 gm/m$^2$ | 43.7 | 22.4 | |

[a]data available in 63 patients; [b]data available in 23 patients only

superior with higher dose [12]. As reported earlier, induction mortality due to infections is a major issue which compromised outcomes [5, 6].

The CR rate after induction was 60% which is similar to other reports from India. This is lower than CR rates reported from Western studies [12, 13]. Currently it is believed that optimum induction outcomes are realized by delivering at least 250–270 mg/m2 of daunorubicin [14]. Most of our patients treated prior to 2011 had undergone only a single course of induction at 60 mg/m$^2$ (cumulative dose-180 mg/m$^2$of daunorubicin). Once we switched to 90 mg/m$^2$, our CR rate improved to 83% without an increase in induction mortality. However, there was no difference in CR rates between same doses in a more recent randomized control trial from the west [12]. Caution is required in interpretation of our data on 90 mg/m$^2$ as it was selectively administered to younger, fitter patients.

The induction mortality of the whole group was 17% which was comparable with data from various centres from India (Table 3). Majority of the mortality was due to infections, which were mainly due to invasive fungi between 2010–2012 and gram negative bacteriae in the subsequent period [5]. However, it must be noted that this report involves patients treated till 2014 and hence excludes the later period where there was a surge in MDR gram negative infections at our center which we had reported separately [5]. We had switched from a policy of using fluconazole as prophylaxis to voriconazole in 2012 which significantly reduced the invasive fungal infection related mortality [15].

The overall survival at 2 years was 30% (Fig. 2). The high induction mortality as well as subsequent relapses contributed to the poor OS seen in our patients. The induction mortality in our study was 17% compared to 5% in Western data from clinical trials [12]. Good risk patients constituted about 24% in our study which was 21.6% in another Indian study compared to 9–15% of the total study population in Western trials [12, 13, 16]. Also, we did not have *FLT3*–ITD and *NPM1* data available in majority of our patients, which may have helped us to risk stratify better. Very few of the intermediate and high risk patients underwent allogenic stem cell transplant in CR1 as is the current standard of care. The outcomes in good risk patients was 66% (Overall survival at 2 years), as compared to > 80% in randomized trials [12]. However, the intermediate and poor risk categories did very poorly (2 year Overall survival of 29% and 26% respectively) (Fig. 3). Better access to allogenic transplants could have potentially improved the survival of these categories. The dose of cytarabine in consolidation did not make a significant impact on survival in our analysis, which has been shown earlier (Fig. 3) [13]. On univariate analysis, the factors which are related to poor survival were WBC count > 1,00,000/cmm presentation, *FLT3*–ITD mutation positivity, and lesser daunorubicin dose in induction (Table 2).

This analysis is retrospective with its inherent limitations. However, this is a presentation of the current outcomes with AML from Indian conditions and shows the long strides required in this area. Since this a relatively rare condition from a public health perspective and requires huge monetary inputs for treatment, most of the patients who come to the out-patient don't receive further therapy and their survival figures are not available. Cytogenetic

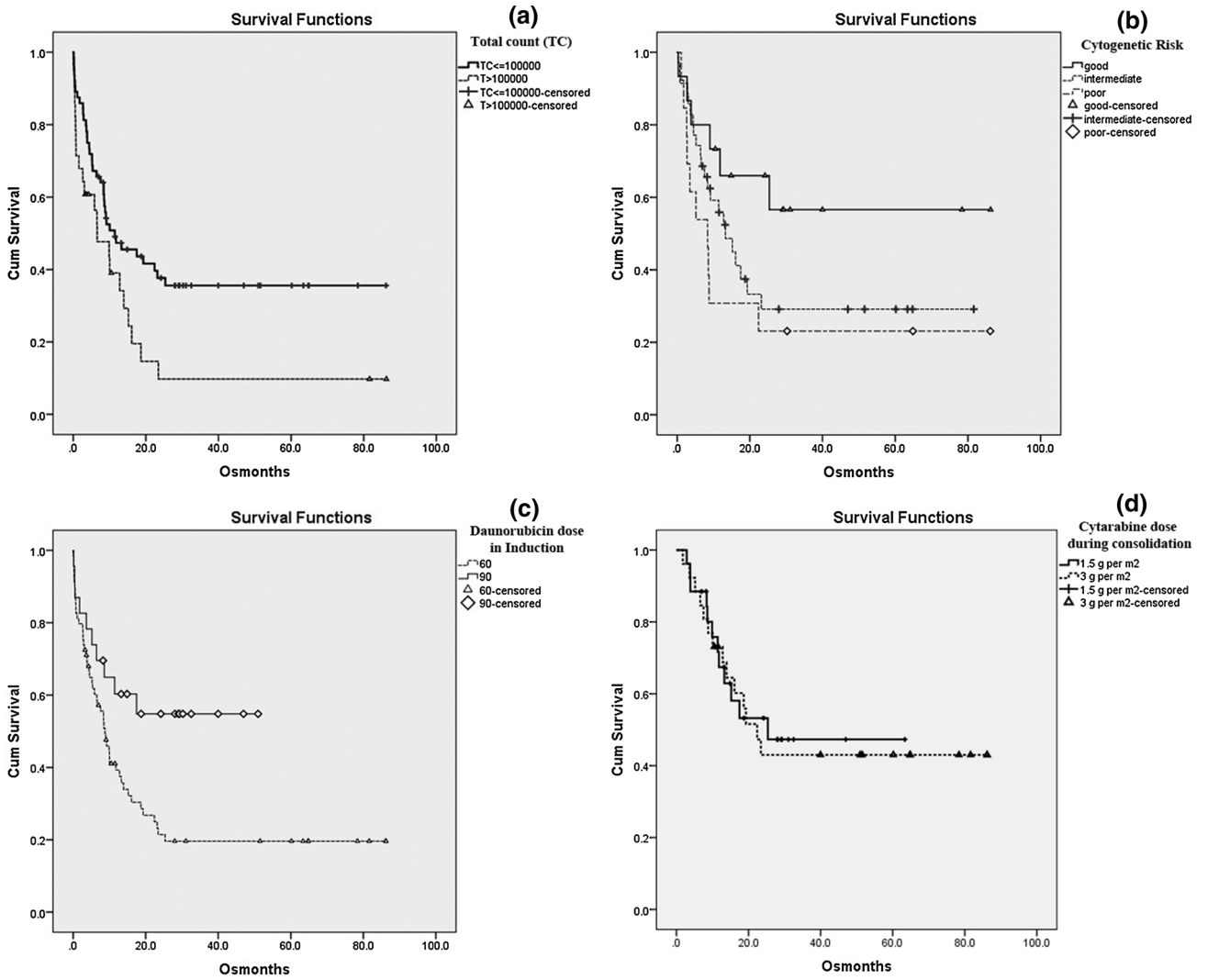


**Fig. 3** Overall survival graphs of patients of AML. **a** Comparing outcomes based in white blood cell count at presentation- $\geq$ 100,000 (bold line) versus < 100,000/cmm (dotted line). **b** Comparing outcomes based in baseline conventional cytogenetic risk classification (N = 63) as low risk (bold line), intermediate risk (dotted line) and high risk (dashed line). **c** Comparing the outcomes based in the dose of daunorubicin in induction 90 mg/m$^2$ (bold line) versus 60 mg/m$^2$ (dotted line), **d** Comparing the outcomes based on the dose of cytarabine in consolidation 1.5 g/m$^2$ (bold line) vs 3 g/m$^2$ (dotted line)

**Table 3** Comparison of outcomes in AML reported from other Indian centers

| | N | Age (years) | Induction mortality (%) | CR rates (%) | Survival (%) |
|---|---|---|---|---|---|
| Philip et al. CMC, Vellore [6] | 68 | 15–60 | 24.7 | NR | 56 (OS, 1 year) |
| Bahl et al. AIIMS, New Delhi [12] | 407 | 8–60 | 18.7 | 70 | 35 (OS, 5 year) |
| Saikia et al. TMH, Mumbai [13] | 166 | 15–60 | 16 | 70 | 22 (EFS, 3 year) |
| Our data | 93 | 19–63 | 17 | 60 | 29 (OS, 2 year) |

Risk, *FLT3*–ITD mutation status, total WBC count at presentation, daunorubicin dose at induction—all these made a statistically significant impact on the survival of the AML patients as per this analysis. There is a need for a prospective database of all AML patients in our country to

understand the survival outcomes better. This can help to initiate future research.

**Acknowledgement** We also acknowledge the support from the tumour registry headed by Dr.Swaminathan, who had helped us in recording and retrieving this data.

**Funding** There were no external sources of funding for this project.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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