ORIGINAL ARTICLE

Treatment patterns and a prognostic scoring system for elderly acute myeloid leukemia patients: a retrospective multicenter cohort study in China

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ABSTRACT   **Objective:** Acute myeloid leukemia (AML) is primarily a malignant disorder affecting the elderly. We aimed to compare the outcomes of different treatment patterns in elderly AML patients and to propose a prognostic scoring system that could predict survival and aid therapeutic decisions.

Methods: Patients aged $\geq$ 60 years who had been diagnosed with AML at 7 hospitals in China were enrolled (n = 228). Treatment patterns included standard chemotherapy, low intensity therapy, and best supportive care (BSC).

Results: The early mortality rates were 31%, 6.8%, and 6.3% for the BSC, low intensity therapy, and standard chemotherapy groups, respectively. The complete remission rate of the standard chemotherapy group was higher than that of the low intensity therapy group. The median overall survival (OS) was 561 days and 222 days for the standard chemotherapy and low intensity therapy groups, respectively, and were both longer than that of the BSC group (86 days). Based on multivariate analyses, we defined a prognostic scoring system that enabled classification of patients into 3 risk groups, in an attempt to predict the OS of patients receiving chemotherapies and low intensity therapies. Low and intermediate risk patients benefited more from standard chemotherapies than from low intensity therapies. However, the median OS was comparable between standard chemotherapies and low intensity therapies in high risk patients.

Conclusions: Our prognostic scoring system could predict survival and help select appropriate therapies for elderly AML patients. Standard chemotherapy is important for elderly AML patients, particularly for those categorized into low and intermediate risk groups.

KEYWORDS   Acute myeloid leukemia; chemotherapy; comorbidity; elderly; geriatric assessment

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. The incidence of AML increases with age, with a median age at diagnosis of 68–72 years[1-3]. Thus, AML is primarily a malignant disorder of the elderly. A diagnosis of AML predicts the shortest median overall survival (OS: 2.67 months) and the lowest estimated 1 year OS (21.8%) by cancer type when diagnosed at ages $\geq$ 65 years[3]. Thus, elderly AML patients should be carefully managed.

Chemotherapy is the fundamental therapy for AML, and complete remission (CR) and long-term survival mostly requires standard chemotherapy[4-6]. However, considering that the benefits of chemotherapy might be compromised by chemotherapeutic toxicities, the proportion of patients intended to receive intensive chemotherapies has decreased with age, with more than 50% of the elderly AML patients

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not receiving chemotherapies[5,6]. In addition, the median OS of the elderly AML patients receiving chemotherapy was only 6 months in a population-based study (n = 5,480)[7]. However, to the best of our knowledge, no study has compared the efficacies of standard chemotherapy and best supportive care (BSC) in elderly patients with AML in China, so knowledge about the benefits of standard chemotherapies compared to BSC for Chinese patients is still unclear.

In addition, identifying patients who would be suitable to receive standard chemotherapy was another critical factor to improve the survival of elderly AML patients[8]. Geriatricians developed geriatric assessment (GA) methods for elderly patients with cancers[9,10], and several studies have shown that GA could predict the clinical outcomes of AML patients[11-17]. However, there is no single gold standard measure of GA in AML patients. In addition, GA does not include the disease characteristics (e.g., hyperleukocytosis) in elderly AML patients. Thus, there is no well-accepted, comprehensive model that considers both patient and disease characteristics in therapeutic decisions for elderly AML patients. In addition, emerging new drugs have played an increasingly important role in the treatment of AML, providing another therapeutic option for elderly AML patients[18]. The toxicities of these drugs are relatively less, and most of them are well-tolerated (i.e., low intensity therapy). A large data analysis of treatment patterns and outcomes among elderly AML patients showed that the median OS of low intensity therapy was better than that of BSC but poorer than that of standard chemotherapy in the United States[6]. However, the role of low intensity therapy in elderly AML patients has not been definitely identified in China.

In this multicenter study, we therefore aimed to compare the efficacies of different treatment patterns in elderly AML patients. We also proposed a prognostic scoring system that could predict survival and help therapeutic decisions for these patients.

Materials and methods

Study population

This was a retrospective multicenter cohort study of elderly patients with AML (non-acute promyelocytic leukemia) at 7 hospitals in Beijing, China (Beijing Hospital, Peking University Third Hospital, Beijing Tongren Hospital, Beijing No. 6 Hospital, Beijing Luhe Hospital, Fuxing Hospital, and Beijing

Chao-Yang Hospital). We included patients with ages ≥ 60 years who had been diagnosed with AML between April 1, 2010 and June 30, 2019. Patients without complete medical information were excluded. The final follow-up visits for survival analyses were conducted on March 31, 2020. The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Local Ethics Committees of each participating hospital (Approval No. 2018BJYYEC-154-02). Sixty patients had been previously reported[19] and all of them were followed-up in the present study.

Data collection

We retrospectively reviewed the medical records that had been collected at the time of diagnosis of leukemia, including age, gender, diagnosis, cytogenetics, white blood cell, hemoglobin, platelet, serum albumin, serum creatinine, Eastern Cooperative Oncology Group (ECOG) performance status (range: 0–5), instrumental activities of daily living (IADL) scales (range: 0–8, higher score indicated less need for assistance)[20], activity of daily living scales (ADL; range: 0–6; a higher score indicated less need for assistance)[21], Charlson Comorbidity Index (CCI)[22], and Mini-mental State Examination (MMSE; using 26 as the cut-off point)[23,24]. Only patients who had all of the above medical information were included in the study (**Supplementary Figure S1**).

As previously reported, Liu et al.[19,25] proposed the IACA index, which could predict the clinical outcomes of elderly patients with diffuse large B-cell lymphoma (DLBCL) and AML. The IACA index included the following variables: IADL scales (8 *vs.* 6–7 *vs.* ≤ 5), age (> 75 years *vs.* ≤ 75 years), comorbidities (CCI score of ≥ 3 *vs.* < 3), and hypoalbuminemia (< 3.4 g/dL *vs.* ≥ 3.4 g/dL). Patients were categorized into low (0 points), intermediate (1–2 points), and high risk (≥ 3 points) groups (**Supplementary Table S1**)[19].

Treatments

Standard chemotherapy protocols for induction therapy always consists of an anthracycline plus cytosine arabinoside ("3 plus 7", or similar), according to Chinese guidelines and estimated patient status[26]. However, the choice of chemotherapy protocols should also be based on each center's competence and experience. Thus, the chemotherapy protocols varied by center in the present study. Patients could also receive

low intensity therapies, which included hypomethylating agent (HMAs)-based therapies or targeted drugs. If the patients did not want to receive standard induction chemotherapies or low intensity therapies, they were given BSC to maximize their quality of life. Hydroxycarbamide or low dose cytarabine to reduce the leukocyte count in patients with hyperleukocytosis was also considered as BSC. Patients were required to receive a medical evaluation at each center or the local hospital at least once a month.

Definitions and assessments

Toxicities of therapies were rated according to the World Health Organization criteria[27]. High leukocyte counts at diagnosis were defined as $\geq 50 \times 10^9$ cells/L. The cytogenetic classification was based on the National Comprehensive Cancer Network criteria[28]. Response evaluation was in accordance with the common international criteria[29]. Early mortality was defined as death within 8 weeks after AML initial diagnosis[5,7]. OS was defined as the time from the date of diagnosis to the date of death from any cause or last follow-up for censored patients. Patients without OS events were censored based on the last date with valid information for the end points.

Statistical analysis

Continuous variables were compared using the Mann-Whitney U test; while categorical variables were compared using χ^2 and Fisher's exact tests. The probabilities of OS were calculated using the Kaplan-Meier estimator. Hazard ratios (HRs) for OS were estimated using Cox proportional hazards regression with a backward stepwise model selection approach. Factors included in the regression model were gender (female vs. male), hyperleukocytosis at diagnosis ($\geq 50 \times 10^9$ cells/L vs. $< 50 \times 10^9$ cells/L)[30], secondary AML (yes vs. no), cytogenetics (poor vs. intermediate vs. favorable), ECOG performance status (≥ 2 vs. < 2), ADL (≤ 4 vs. 6 vs. 5), MMSE (≤ 26 vs. > 26), IACA index (high risk vs. intermediate risk vs. low risk), and therapy patterns (standard chemotherapy vs. low intensity therapy vs. BSC). All reported P-values were based on two-sided tests, and significance was set at $P = 0.05$. Data analyses were primarily conducted using SPSS statistical software for Windows (SPSS, Chicago, IL, USA) and the R-software package, version 3.6.2; (http://www.r-project.org).

Results

Patient characteristics

We enrolled 228 patients (**Table 1**; **Supplementary Figure S1**). Among the patients receiving low intensity therapy, most of them received decitabine-based therapies ($n = 42$) while the others received sorafenib ($n = 1$) or venetoclax ($n = 1$) as monotherapies. The characteristics of comorbidities are shown in **Supplementary Table S2**.

Early mortality, toxicities, and CR

Patients who received BSC had the highest rate of early mortality (31%). However, the early mortality rates were comparable between the standard chemotherapy (6.3%) and low intensity therapy groups (6.8%). A similar situation was observed in patients aged 60–75 years and > 75 years (**Figure 1A**).

Patients who received standard induction chemotherapies showed higher rates of grade ≥ 3 hematological toxicities (99.3% vs. 90.9%; $P = 0.012$) and any grade ≥ 3 toxicities (99.3% vs. 93.2%; $P = 0.042$) compared with those who received low intensity therapies. The occurrences of other toxicities were comparable between the groups (**Figure 1B**).

The CR rate was significantly higher in patients who received standard chemotherapies compared with those who received low intensity therapies, particularly in those older than 75 years (**Figure 1C**).

OS

The median OS of the total population was 293 days [95% confidence interval (CI): 213–373 days]. The median OS was 561 days (95% CI: 471–650 days) and 222 days (95% CI: 165–279 days) for the standard chemotherapy and low intensity therapy groups, respectively, which were both significantly longer than that of the BSC group (86 days, 95% CI: 65–107 days; **Figure 2A**). In patients who were 60–70 years old, the OS of the standard chemotherapy and low intensity therapy groups was better than that of the BSC group (**Figure 2B**). In those older than 75 years, only the standard chemotherapy group showed better OS than the BSC group (**Figure 2C**).

Using multivariate analysis, receiving standard chemotherapy improved the OS compared with those receiving BSC. Besides the treatment patterns, IACA intermediate and high

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Table 1 Patient characteristics

Characteristics	Total (n = 228)
Age at diagnosis (years)	71 (60–91%)
Gender	
Male	143 (62.7%)
Female	85 (37.3%)
ADL score	
6	168 (73.7%)
5	26 (11.4%)
≤ 4	34 (14.9%)
IADL score	
8	119 (52.2%)
6–7	58 (25.4%)
≤ 5	51 (22.4%)
ECOG score, ≥ 2	83 (36.4%)
MMSE score, ≤ 26	73 (32.0%)
Charlson Comorbidity Index, ≥ 3	36 (15.8%)
WBC at diagnosis (10^9 cells/L)	7.5 (0.3–460.3)
WBC at diagnosis, ≥ 50 × 10^9 cells/L	51 (22.4%)
Hemoglobin at diagnosis, (g/L)	80 (36–159)
Platelet at diagnosis, (10^9 cells/L)	52 (2–1,559)
FAB Subtype	
M0	4 (1.8%)
M1	10 (4.4%)
M2	138 (60.5%)
M4	44 (19.3%)
M5	26 (11.4%)
M6	6 (2.6%)
Cytogenetic at diagnosis	
Favorable	14 (6.1%)
Intermediate	178 (78.1%)
Poor	36 (15.8%)
Secondary AML	48 (21.1%)
Serum albumin at diagnosis (g/dL)	3.7 (2.2–8.8)
Serum albumin < 3.4 (g/dL)	65 (28.5%)
Serum creatinine at diagnosis (µmol/L)	79 (33–567)

Table 1 Continued

Characteristics	Total (n = 228)
IACA index†	
Low risk (score 0)	61 (26.8%)
Intermediate risk (score 1 to 2)	114 (50.0%)
High risk (score ≥ 3)	53 (23.2%)
Therapies	
Best supportive care	42 (18.4%)
Low-intensity therapy‡	44 (19.3%)
Standard chemotherapy	142 (62.3%)
Duration of follow-up (days)	265 (3–4,075)

Data was present as n (%) or median (range). ADL, activities of daily living; AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; IADL, instrumental activity of daily living; IACA index, IADL scales, Age, Comorbidities, and Albumin index; MMSE, Mini-mental State Examination; WBC, white blood cell. †IACA index included the following variables: age (> 75 years vs. ≤ 75 years), IADL scale (8 vs. 6 to 7 vs. ≤ 5), hypoalbuminemia (< 3.4 g/dL vs. ≥ 3.4 g/dL), and comorbidities (CCI score of ≥ 3 vs. < 3). Patients were categorized into low (0 point), intermediate (1–2 points), and high risk (≥ 3 points) groups. ‡Low intensity therapy included decitabine-based therapies (n = 42), sorafenib alone (n = 1), and venetoclax alone (n = 1).

risk status, male sex, and hyperleukocytosis at diagnosis were independently associated with a poorer OS (**Figure 3**).

Prognostic scoring systems for elderly AML patients

We proposed a prognostic scoring system based on the results of multivariate analysis. A weighted score of 1 was assigned to male sex, IACA intermediate risk status, and hyperleuko-cytosis at diagnosis, and a weighted score of 2 was assigned to IACA high risk status. The overall score ranged from 0–4, with higher scores indicating greater risk. The survival rates were comparable between groups with scores of 0–1 and scores of 3–4 (data not shown). Based on these findings, we created a 3 category system: low risk, score ≤ 1; interme-diate risk, score 2; and high risk, score ≥ 3. Among the 186 patients who received therapies, 79, 77, and 30 patients were categorized into low, intermediate, and high risk groups, respectively.
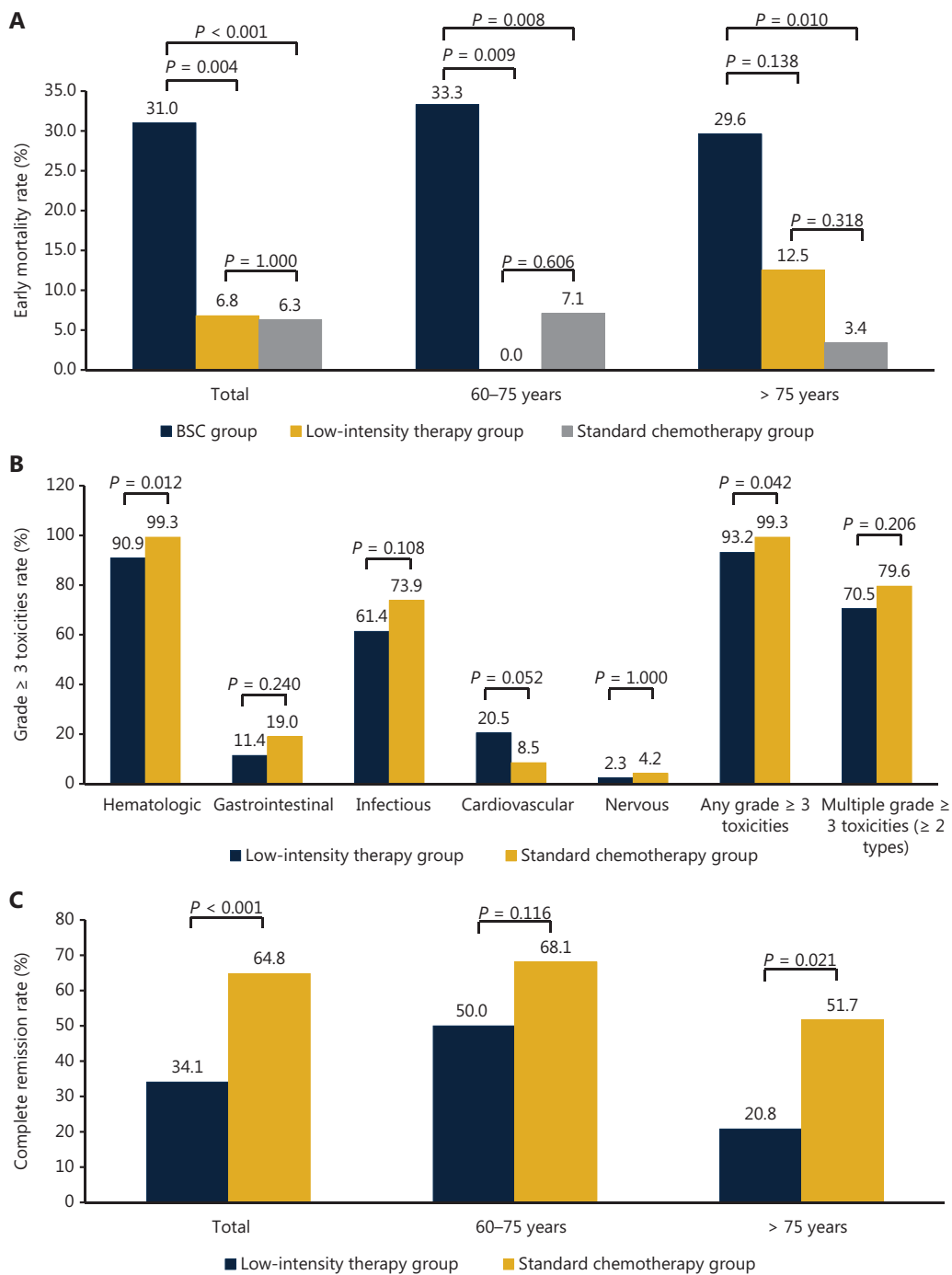
Figure 1   Early mortality, therapeutic toxicities, and complete remission after different treatment patterns of (A) early mortality (B) therapeutic toxicities, and (C) complete remission.

The efficacy of the prognostic scoring system for elderly AML patients

Among the patients receiving standard chemotherapies, the median OS was 711 days (95% CI: 449–973 days) and 406 days (95% CI: 172–640 days) for the low risk and intermediate risk groups, respectively ($P = 0.012$), which were both significantly longer than that in the high risk group (176 days; 95% CI: 0–373 days; **Figure 4A**). Among the patients receiving low intensity therapies, the patients in the low risk group
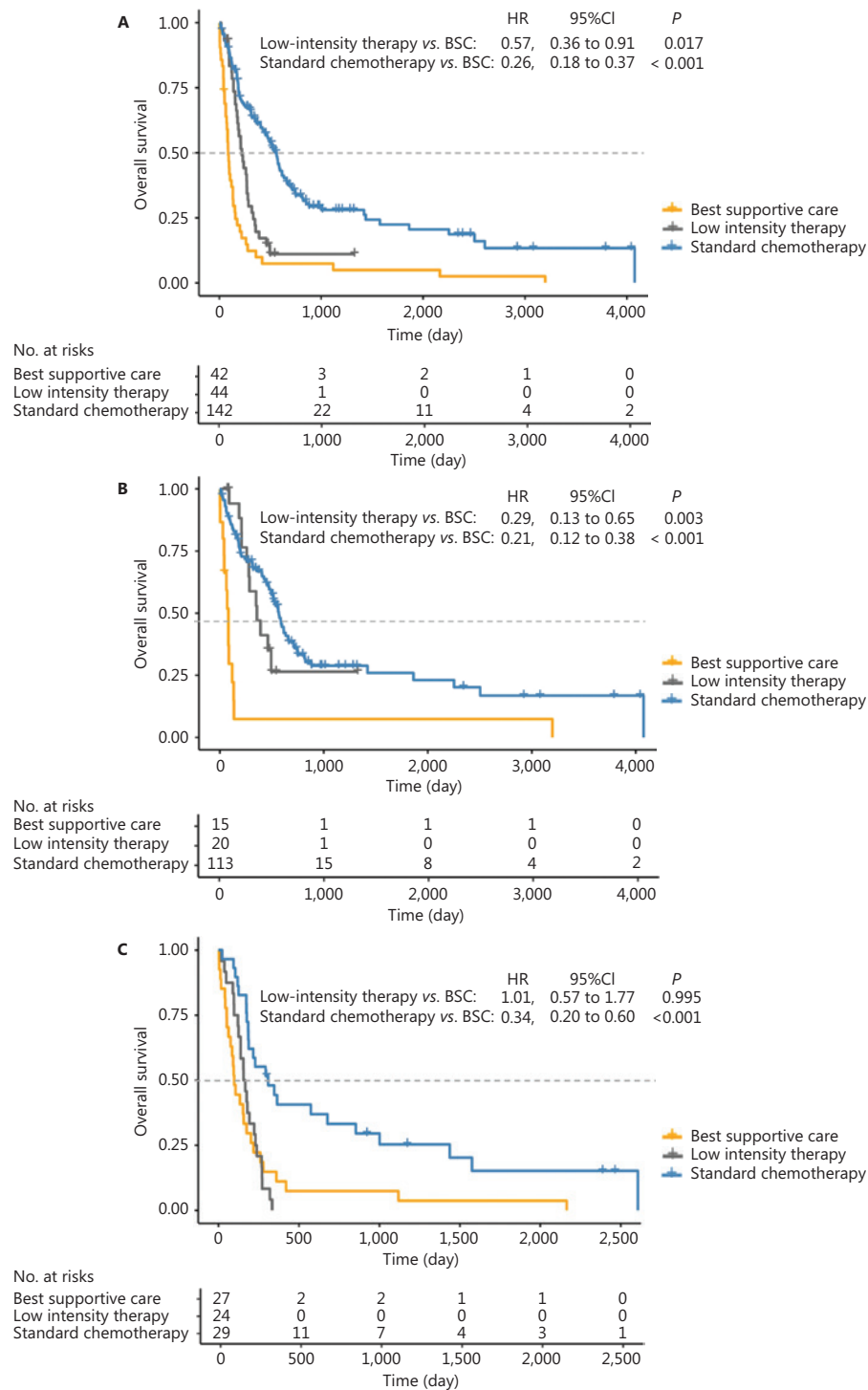
Figure 2 Overall survival after different treatment patterns of (A) total patients, (B) 60–75 years, and (C) beyond 75 years.

also showed the longest OS, and the median OS was comparable between the intermediate risk and high risk groups (**Figure 4B**).

Among patients in the low and intermediate risk groups, the CR rate of the standard chemotherapy group was significantly higher than that of the low intensity therapy group (67.7% vs. 37.5%; $P = 0.002$). The median OS of the standard chemotherapy group (573 days; 95% CI: 485–661 days) was significantly longer than that of the low intensity therapy group (260 days; 95% CI: 179–341 days; $P < 0.001$).
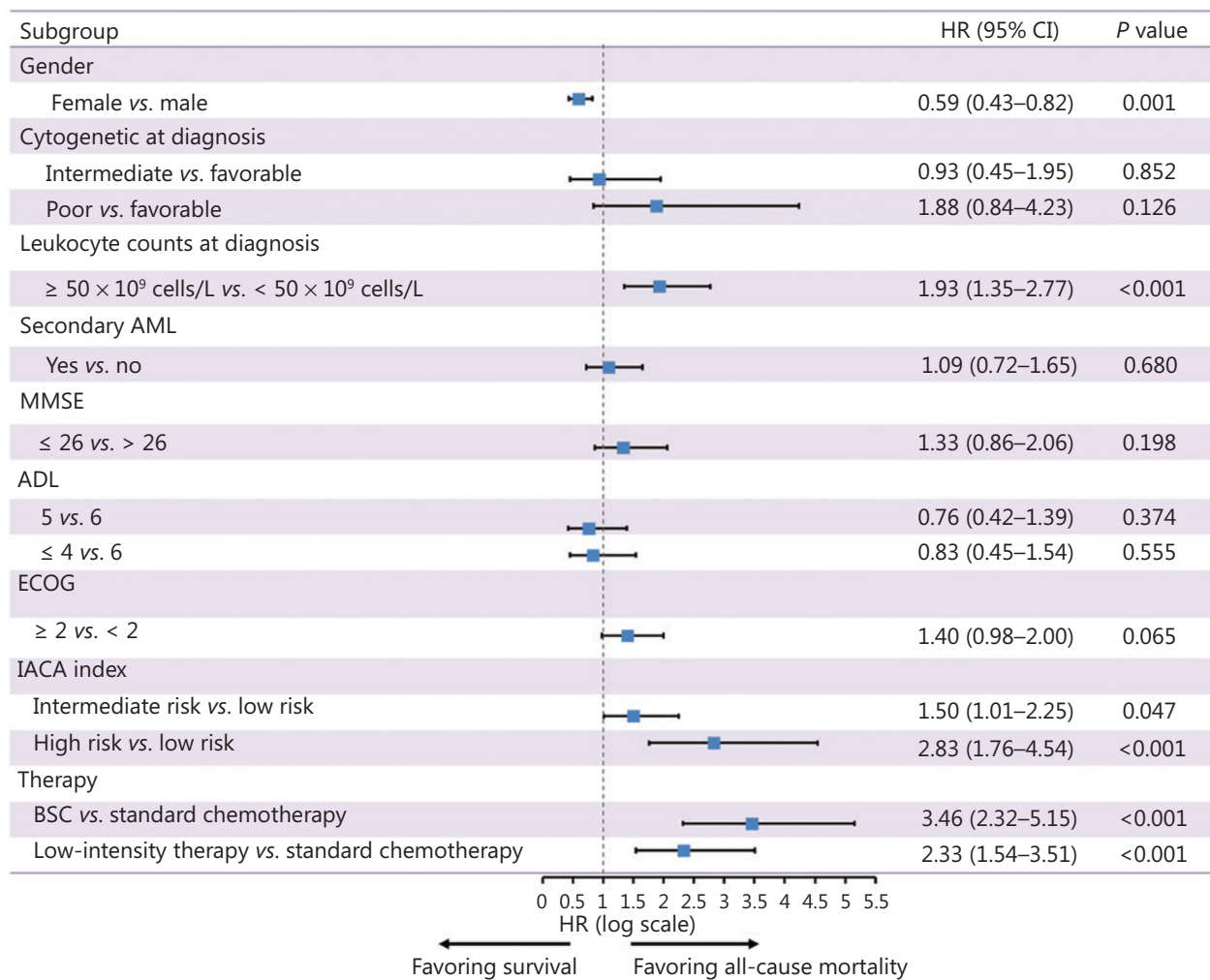
Subgroup	HR (95% CI)	P value
Gender		
Female *vs*. male	0.59 (0.43–0.82)	0.001
Cytogenetic at diagnosis		
Intermediate *vs*. favorable	0.93 (0.45–1.95)	0.852
Poor *vs*. favorable	1.88 (0.84–4.23)	0.126
Leukocyte counts at diagnosis		
$\geq 50 \times 10^9$ cells/L *vs*. $< 50 \times 10^9$ cells/L	1.93 (1.35–2.77)	<0.001
Secondary AML		
Yes *vs*. no	1.09 (0.72–1.65)	0.680
MMSE		
≤ 26 *vs*. > 26	1.33 (0.86–2.06)	0.198
ADL		
5 *vs*. 6	0.76 (0.42–1.39)	0.374
≤ 4 *vs*. 6	0.83 (0.45–1.54)	0.555
ECOG		
≥ 2 *vs*. < 2	1.40 (0.98–2.00)	0.065
IACA index		
Intermediate risk *vs*. low risk	1.50 (1.01–2.25)	0.047
High risk *vs*. low risk	2.83 (1.76–4.54)	<0.001
Therapy		
BSC *vs*. standard chemotherapy	3.46 (2.32–5.15)	<0.001
Low-intensity therapy *vs*. standard chemotherapy	2.33 (1.54–3.51)	<0.001

HR (log scale)
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5

← Favoring survival   Favoring all-cause mortality →

Figure 3 Hazard ratios and 95% confidence intervals for overall survival using multivariate analysis.

However, the median OS was comparable between the low intensity therapy and BSC groups (136 days; 95% CI: 94–178 days; **Figure 5A**). Thus, these patients could benefit from standard chemotherapies.

Among the patients in the high risk group, the CR rate was comparable between standard chemotherapy and low intensity therapy groups (44.4% *vs*. 25.0%; $P = 0.442$). The median OS was comparable between the standard chemotherapy (176 days; 95% CI: 0–373 days) and low intensity therapy group (125 days; 95% CI: 27–223 days; $P = 0.109$), which were both significantly better than that of the BSC group (63 days: 95% CI: 27–99 days; **Figure 5B**). Hence, these patients could benefit from either standard chemotherapy or low intensity therapy, although the OS was still unsatisfactory.

Discussion

In the present study, we found that standard chemotherapy and low intensity therapy improved survival compared with those receiving only BSC, and even in some very old patients (> 75 years). To the best of our knowledge, this was the largest multicenter study identifying the up-to-date undefined role of standard chemotherapy, low intensity therapy, and BSC in elderly Chinese AML patients. In addition, we proposed a comprehensive prognostic scoring system that could predict the OS and aid in therapeutic decisions in elderly AML patients. We could also identify a subset of elderly AML patients who would benefit more from standard chemotherapy.

In the present study, elderly AML patients who received BSC showed very poor clinical outcomes. Approximately 30% of
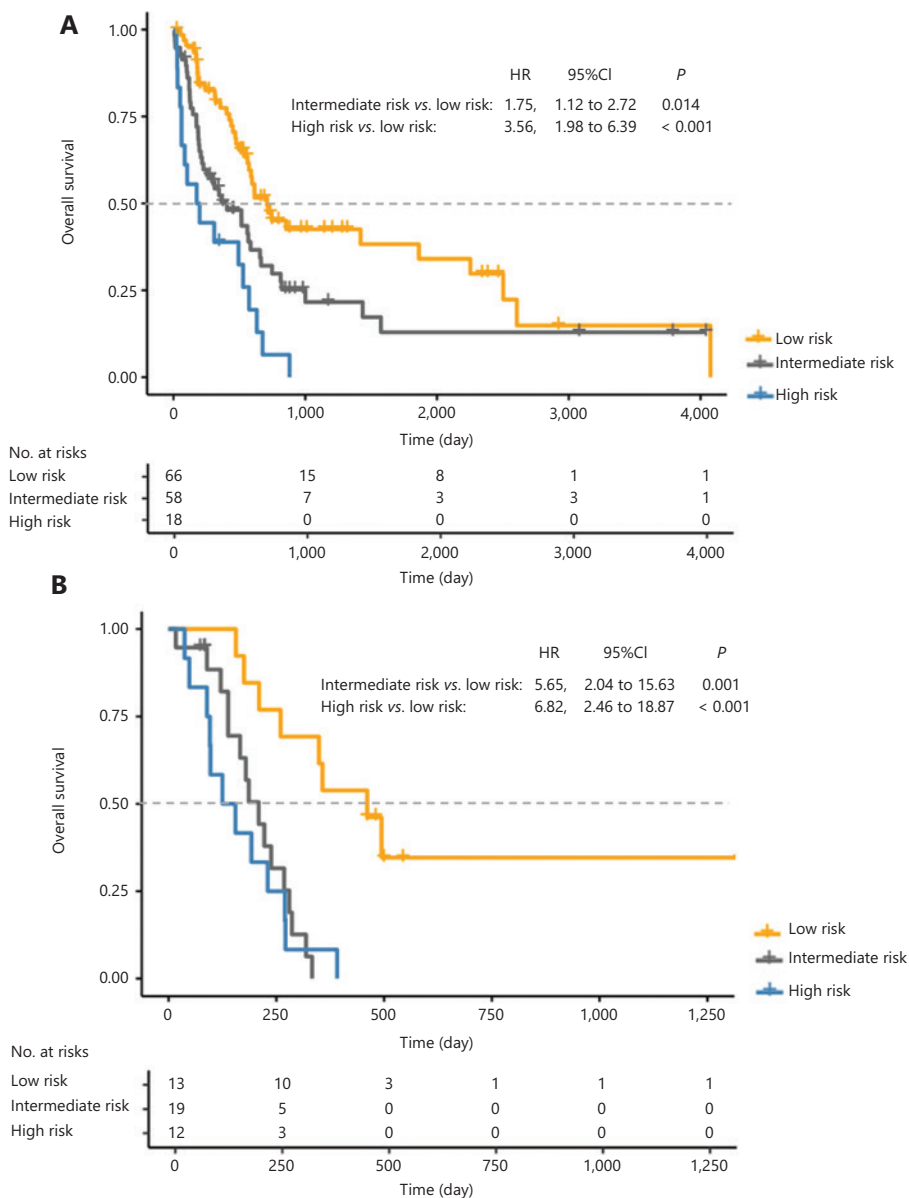
Figure 4 Prognostic scoring system predicted the overall survival of elderly acute myeloid leukemia patients, including (A) the standard chemotherapy group and (B) the low intensity therapy group.

these patients died within 8 weeks, and the median OS was only 86 days. Similarly, previous studies reported that the median OS of patients receiving BSC was only 1.5 months, 1.2 months, and 2.4 months in the United States[6], India[31], and Singapore[32], respectively. Because this therapeutic technique has been significantly improved, elderly AML patients should avoid receiving BSC alone in China.

Miura et al.[33] proposed the ACA index, including very old age (> 75 years), hypoalbuminemia, and medical comorbidities, which could predict the OS of DLBCL patients. Based

on this index, Liu et al.[25] proposed a new prognostic model, including IADL scales, and ACA index (IACA index), which could reflect the tolerance of intensive chemotherapies and predict the clinical outcomes of elderly DLBCL patients more effectively. In addition, Zhang et al.[19] observed that the IACA index could also predict the clinical outcomes of elderly AML patients in a pilot study. In this multicenter study, the IACA index was one of the independent prognostic factors in the multivariate analysis. Advanced age at diagnosis is an important factor that could influence the survival of elderly AML
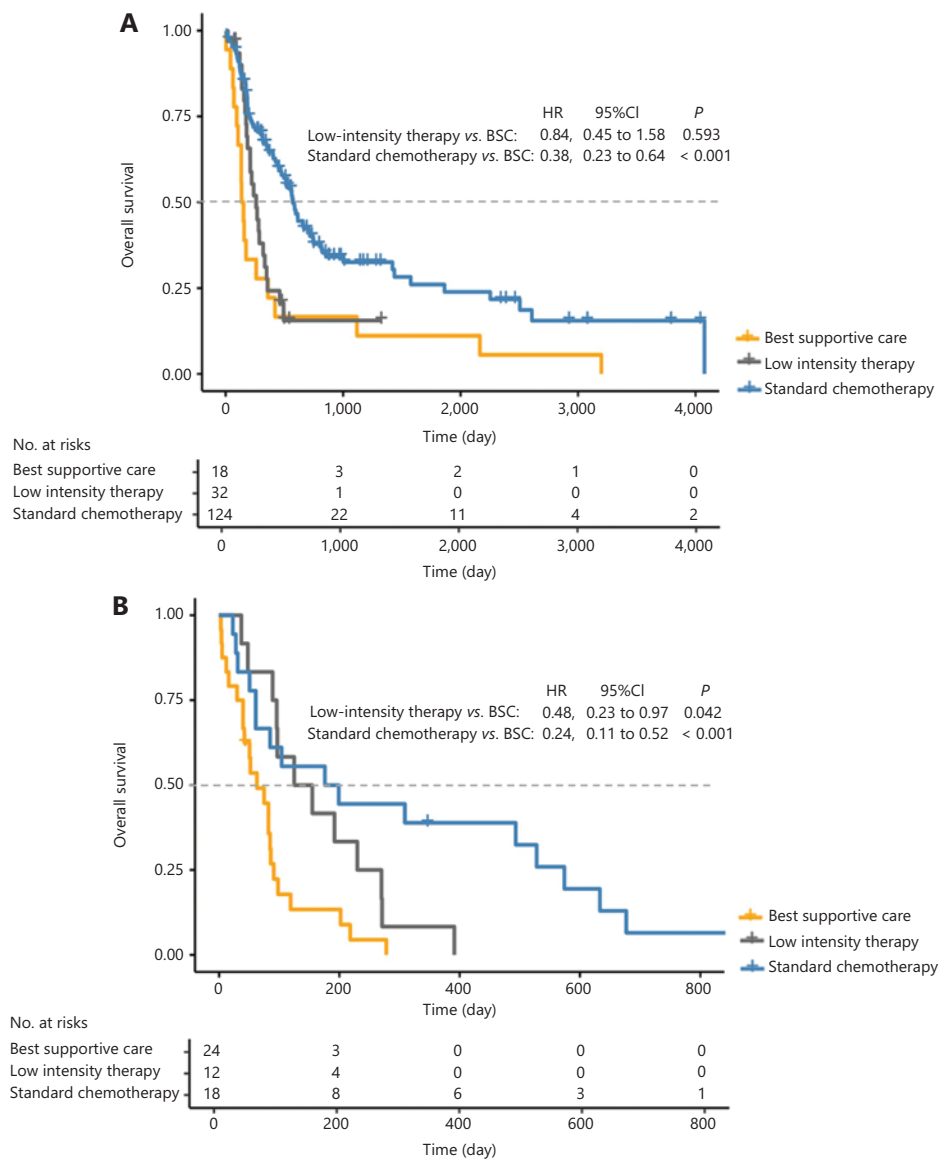
Figure 5 Overall survival after different treatments according to the prognostic scoring system for (A) the low and intermediate risk group, and (B) the high risk group.

patients[3,34]. Moreover, the IACA index was used to evaluate the functional status (IADL scale), nutritional status (serum albumin), and comorbidities (CCI score), which were all the key components of GA. Thus, the IACA index could consider both chronological and biological age.

Our prognostic scoring system included other variables. Hyperleukocytosis at diagnosis was associated with a higher risk of early death, which also led to a higher probability of relapse and death in the long run[30,35,36]. Thus, AML patients with hyperleukocytosis had a particularly poor prognosis. In addition, gender of patients was also associated with OS. Based

on a dataset of 4,865 patients diagnosed with AML, Hossain et al.[37] observed that females showed a significant survival advantage over their male counterparts.

Thus, our prognostic scoring system including the leukemia burden, demographic characteristics, and GA, could comprehensively reflect the status of elderly AML patients. In particular, most of the contents were objective, which could help complete the evaluations more accurately. In addition, this prognostic scoring system was easy to use and could be completed in a short time. Owing to the shortage of physicians and long waiting time for visitors, treatment has become one

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of the critical challenges in China[38], so this concise scoring system could be easily popularized, particularly for doctors from general hospitals or community clinics.

For the low and intermediate risk patients in our prognostic scoring system, they might not have hyperleukocytosis. Even if they had, the tolerance of intensive therapies was relatively good (IACA low and intermediate risk). Thus, these patients could benefit more from standard chemotherapy, which could improve both the CR rate and long-term survival. It is suggested that advanced age alone is not an absolute contraindication to standard chemotherapies. For high risk patients, most may have both hyperleukocytosis and poor tolerance to intensive therapies, and therapeutic decisions should balance leukemic clearance and therapeutic toxicities. We observed that the disparity of OS between low intensity therapy and standard chemotherapy was not significant in high risk patients. Considering the toxicities of standard chemotherapy, low intensity therapy might be reasonable for these patients. However, the OS of standard chemotherapy and low intensity therapy was still unsatisfactory.

Emerging new drugs provide alternative therapeutic options for elderly AML patients[39]. HMAs have been identified in elderly AML patients who were not fit to receive standard chemotherapy, with a median OS of 5.5–9 months and a 1 year survival rate of 28%[6,7,40-42]. FLT3 inhibitors[43,44], Bcl-2 inhibitors[45], and IDH2 inhibitors[46] could also be used as monotherapies in elderly AML patients. Recently, excellent outcomes of several combination therapies have been reported, particularly venetoclax combined with HMAs[47]. The median duration of CR was 11.3 months and the median OS was 17.5 months[48]. However, venetoclax has not yet been commercially available in China. Therefore, only 1 patient received venetoclax as monotherapy in the present study. In addition, all trans-retinoic acid in combination with decitabine[49,50] and azacitidine in combination with nivolumab[51,52] also have appeared to be safe and effective therapies for elderly AML patients. However, none of the patients received these combination therapies in the present study. New drugs could play a bigger and better role in the treatment of elderly AML patients, particularly for high risk patients according to our prognostic scoring system, because of their poor tolerance to standard chemotherapies. Knowing that the sample of patients receiving low intensity therapies was relatively small and many new drugs were not included, it would be premature to make conclusions regarding the superiority of standard chemotherapies over low intensity therapies in the present study. In the future, prospective randomized controlled trials could further compare the efficacy and safety of standard chemotherapies and new drugs in elderly AML patients.

This study had several limitations. First, it was a retrospective study, which might have influenced the accuracy of our findings. Second, patients received different therapeutic regimens in the present study, and prospective studies using unified therapeutic regimens could help to further identify the efficacy of our prognostic scoring system.

Conclusions

We found that the clinical outcomes of patients receiving BSC were poorer than standard chemotherapy. Standard chemotherapy could improve survival, and advanced age alone was not an absolute contraindication. Our prognostic scoring system, which is a concise but comprehensive model, could predict survival and help select appropriate therapies for elderly AML patients. Standard chemotherapy is important for elderly AML patients, particularly for those categorized into low and intermediate risk groups. Considering that only a limited number of new drugs are commercially available in China, the present study has important practical significance.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xiaodong Mo, Hongmei Jing, and Hui Liu.

Collected the data: Chunli Zhang, Wei Wan, Shuai Zhang, Jingwen Wang, Ru Feng, Jiangtao Li, Junyue Chai, Hebing Zhou, Liru Wang, and Yuping Zhong.

Contributed data or analysis tools: Chunli Zhang, Xiaodong Mo, and Mengzhu Shen;

Performed the analysis: Chunli Zhang, Xiaodong Mo, Mengzhu Shen, and Hui Liu.

Wrote the paper: Xiaodong Mo, Chunli Zhang, Hongmei Jing, and Huiliu.

Other contribution: All authors have read and approved the final manuscript.

References

1. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. J Clin Oncol. 2014; 32: 2541-52.

2. Juliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood. 2012; 119: 3890-9.

3. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev. 2019; 36: 70-87.

4. Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. Blood. 2009; 113: 4179-87.

5. Juliusson G. Older patients with acute myeloid leukemia benefit from intensive chemotherapy: an update from the Swedish acute leukemia registry. Clin Lymphoma Myeloma Leuk. 2011; 11(Suppl 1): S54-9.

6. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. Ann Hematol. 2015; 94: 1127-38.

7. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012; 97: 1916-24.

8. Ossenkoppele G, Lowenberg B. How I treat the older patient with acute myeloid leukemia. Blood. 2015; 125: 767-74.

9. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002; 20: 494-502.

10. Monfardini S, Ferrucci L, Fratino L, del Lungo I, Serraino D, Zagonel V. Validation of a multidimensional evaluation scale for use in elderly cancer patients. Cancer. 1996; 77: 395-401.

11. Sherman AE, Motyckova G, Fega KR, Deangelo DJ, Abel GA, Steensma D, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. Leuk Res. 2013; 37: 998-1003.

12. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. 2013; 121: 4287-94.

13. Deschler B, Ihorst G, Platzbecker U, Germing U, Marz E, de Figuerido M, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. Haematologica. 2013; 98: 208-16.

14. Loh KP, Klepin HD. Geriatric assessment in older patients with acute myeloid leukemia. Cancers (Basel). 2018; 10: 225.

15. Rao AV. Fitness in the elderly: how to make decisions regarding acute myeloid leukemia induction. Hematology Am Soc Hematol Educ Program. 2016; 2016: 339-47.

16. Klepin HD, Ritchie E, Major-Elechi B, Le-Rademacher J, Seisler D, Storrick L, et al. Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: report of CALGB 361006 (Alliance). J Geriatr Oncol. 2020; 11: 107-13.

17. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Ellis LR, et al. The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. J Am Geriatr Soc. 2011; 59: 1837-46.

18. Thomas X, Elhamri M, Heiblig M. Emerging pharmacotherapies for elderly acute myeloid leukemia patients. Expert Rev Hematol. 2020; 13: 619-43.

19. Zhang CL, Feng R, Li JT, Wang T, Bai JF, Liu H. A new tool for comprehensive geriatric assessment in elderly patients with acute myeloid leukemia: a pilot study from China. Chin Med J (Engl). 2020; 133: 381-7.

20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9: 179-86.

21. Katz S, Akpom CA. A measure of primary sociobiological functions. Int J Health Serv. 1976; 6: 493-508.

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-83.

23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12: 189-98.

24. Li H, Jia J, Yang Z. Mini-Mental state examination in elderly Chinese: a population-based normative study. J Alzheimers Dis. 2016; 53: 487-96.

25. Liu H, Zhang CL, Feng R, Li JT, Tian Y, Wang T. Validation and refinement of the age, comorbidities, and albumin index in elderly patients with diffuse large B-Cell lymphoma: an effective tool for comprehensive geriatric assessment. Oncologist. 2018; 23: 722-9.

26. Leukemia & Lymphoma Group, Chinese Society of Hematology, Chinese Medical Association. Chinese guidelines for diagnosis and treatment of adult acute myeloid leukemia (not APL). Zhong hua Xue Ye Xue Za Zhi. 2017; 38: 177-82.

27. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981; 47: 207214.

28. Torlen J, Remberger M, Le Blanc K, Ljungman P, Mattsson J. Impact of pretransplantation indices in hematopoietic stem cell transplantation: knowledge of center-specific outcome data is pivotal before making index-based decisions. Biol Blood Marrow Transplant. 2017; 23: 677-83.

29. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003; 21: 4642-9.

30. Stahl M, Shallis RM, Wei W, Montesinos P, Lengline E, Neukirchen J, et al. Management of hyperleukocytosis and impact of leukapheresis among patients with acute myeloid leukemia (AML) on short- and long-term clinical outcomes: a large, retrospective, multicenter, international study. Leukemia. 2020; 34: 3149-60.

31. Kanakasetty GB, Chethan R, Kuntegowdanahalli LC, Dasappa L, Jacob LA, Babu S, et al. Treatment patterns and comparative analysis of non-intensive regimens in elderly acute myeloid leukemia patients – a real-world experience from India. Ann Hematol. 2019; 98: 881-8.

32. Lao Z, Yiu R, Wong GC, Ho A. Treatment of elderly patients with acute myeloid leukemia with azacitidine results in fewer hospitalization days and infective complications but similar survival compared with intensive chemotherapy. Asia Pac J Clin Oncol. 2015; 11: 54-61.

33. Miura K, Konishi J, Miyake T, Makita M, Hojo A, Masaki Y, et al. A host-dependent prognostic model for elderly patients with diffuse large B-Cell Lymphoma. Oncologist. 2017; 22: 554-60.

34. Song X, Peng Y, Wang X, Chen Y, Jin L, Yang T, et al. Incidence, survival, and risk factors for adults with acute myeloid leukemia not otherwise specified and acute myeloid leukemia with recurrent genetic abnormalities: analysis of the surveillance, epidemiology, and End Results (SEER) Database, 2001–2013. Acta Haematol. 2018; 139: 115-27.

35. Greenwood MJ, Seftel MD, Richardson C, Barbaric D, Barnett MJ, Bruyere H, et al. Leukocyte count as a predictor of death during remission induction in acute myeloid leukemia. Leuk Lymphoma. 2006; 47: 1245-52.

36. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood. 2015; 125: 3246-52.

37. Hossain MJ, Xie L. Sex disparity in childhood and young adult acute myeloid leukemia (AML) survival: evidence from US population data. Cancer Epidemiol. 2015; 39: 892-900.

38. WHO. Density of physicians (total number per 1000 population, latest available year). In. https://www.who.int/gho/health_workforce/physicians_density/en/: Accessed 2020.

39. Lai C, Doucette K, Norsworthy K. Recent drug approvals for acute myeloid leukemia. J Hematol Oncol. 2019; 12: 100.

40. Lubbert M, Ruter BH, Claus R, Schmoor C, Schmid M, Germing U, et al. A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. Haematologica. 2012; 97: 393-401.

41. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012; 30: 2670-7.

42. Quintas-Cardama A, Ravandi F, Liu-Dumlao T, Brandt M, Faderl S, Pierce S, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. Blood. 2012; 120: 4840-5.

43. Cortes J, Perl AE, Dohner H, Kantarjian H, Martinelli G, Kovacsovics T, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2018; 19: 889-903.

44. Jia JS, Zhu HH, Fu HX, Gong LZ, Kong J, Huang XJ, et al. Efficacy and safety of sorafenib as monotherapy to FLT3-ITD positive acute myeloid leukemia. Zhonghua Xue Ye Xue Za Zhi. 2016; 37: 1022-6.

45. Huemer F, Melchardt T, Jansko B, Wahida A, Jilg S, Jost PJ, et al. Durable remissions with venetoclax monotherapy in secondary AML refractory to hypomethylating agents and high expression of BCL-2 and/or BIM. Eur J Haematol. 2019; 102: 437-41.

46. Pollyea DA, Tallman MS, de Botton S, Kantarjian HM, Collins R, Stein AS, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. Leukemia. 2019; 33: 2575-84.

47. Pollyea DA, Stevens BM, Jones CL, Winters A, Pei S, Minhajuddin M, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018; 24: 1859-66.

48. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019; 133: 7-17.

49. Lübbert M, Grishina O, Schmoor C, Schlenk RF, Jost E, Crysandt M, et al. Valproate and retinoic acid in combination with decitabine in elderly nonfit patients with acute myeloid leukemia: results of a multicenter, randomized, 2 × 2, Phase II Trial. J Clin Oncol. 2020; 38: 257-70.

50. Wu W, Lin Y, Xiang L, Dong W, Hua X, Ling Y, et al. Low-dose decitabine plus all-trans retinoic acid in patients with myeloid neoplasms ineligible for intensive chemotherapy. Ann Hematol. 2016; 95: 1051-7.

51. Daver N, Garcia-Manero G, Basu S, Boddu PC, Alfayez M, Cortes JE, et al. Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study. Cancer Discov. 2019; 9: 370-83.

52. Stahl M, Goldberg AD. Immune checkpoint inhibitors in acute myeloid leukemia: novel combinations and therapeutic targets. Curr Oncol Rep. 2019; 21: 37.