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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

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. We aimed to validate and refine the Age, Comorbidities, and Albumin (ACA) index in elderly Chinese patients with diffuse large B-cell lymphoma (DLBCL) and propose a more effective method for comprehensive geriatric assessment (CGA).

Materials and Methods. Patients ≥65 years of age who had been diagnosed with de novo DLBCL in the Institute of Hematology, Beijing Hospital, were screened for eligibility (*n* = 99).

Results. Based on the ACA index, 39, 31, 26, and 3 patients were categorized into the "excellent," "good," "moderate," and "poor" groups, respectively. The 2-year treatment-related mortality rate was significantly higher and the survival rates poorer in the ACA "moderate to poor" group compared with those of the ACA "good" and "excellent" groups. Multivariable model

analysis identified two independent predictors of overall survival: the instrumental activities of daily living (IADL) scale and the ACA index. IADL scores of 6 to 7 and the ACA "good" group were assigned 1 point; IADL scores ≤5 and the ACA "moderate to poor" group were assigned 2 points. Based on these data, we created a three-category system (IADL ACA index [IACA index]): low risk, score 0; intermediate risk, score 1 to 2; and high risk, score 3 to 4. The IACA index could effectively discriminate the response rates, overall survival, and progression-free survival rates in elderly patients with DLBCL.

Conclusion. We observed that the ACA index could partially predict the clinical outcomes of elderly DLBCL patients in China. Based on this index, we proposed the IACA index as an effective tool for CGA in DLBCL. *The Oncologist* 2018;23:722–729

Implications for Practice: Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent types of malignant lymphoma in elderly people, and identifying patients suitable for curative therapy is critical in the improvement of clinical outcomes. Recently, some authors proposed the Age, Comorbidities, and Albumin (ACA) index. Combining the use of the instrumental activities of daily living (IADL) scale and the ACA index, this article describes the IADL ACA index (IACA index), which is an effective tool for comprehensive geriatric assessment in DLBCL.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent types of malignant lymphoma in elderly people [1]. In China, in elderly patients (older than 64 years), DLBCL made up approximately half of all lymphomas [2]. Thus, the management of elderly patients with DLBCL is very important.

The wide use of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has significantly improved the clinical outcome of DLBCL even in older patients [3, 4]. However, some elderly patients cannot bear the toxicities related to this therapy, and identifying patients suitable for curative therapy is critical in the improvement of clinical outcomes. Over the last few decades, geriatricians have developed

comprehensive geriatric assessment (CGA) methods for elderly patients, which are useful for the evaluation of patients with cancer [5, 6]. Many authors have suggested that CGA is more effective than clinical judgment in identifying elderly patients with DLBCL who would benefit from aggressive therapy, but the tools used for CGA are varied and not uniform [7]. Recently, Miura et al. [8] proposed the Age, Comorbidities, and Albumin (ACA) index, which is simple to use and has the ability to stratify the prognosis, tolerability to cytotoxic drugs, and adherence to treatment of elderly patients with DLBCL treated with R-CHOP. However, the ACA index does not include evaluation for functional status, which may influence its efficacy.

Thus, we aimed to validate the ACA index in elderly Chinese patients with DLBCL. In addition, we wanted to refine the ACA index and propose a more effective CGA method that could serve as a guide for optimal personalized therapy for elderly patients with DLBCL treated with R-CHOP.

MATERIALS AND METHODS

Patients

In this retrospective study, patients ≥65 years of age who had been diagnosed with de novo DLBCL and had received R-CHOP-based treatments between January 1, 2003, and December 31, 2016, in the Department of Hematology, Beijing Hospital, People's Republic of China, were screened for eligibility. Fifteen patients were excluded because no information on treatments ($n = 4$) or follow-ups ($n = 11$) was available. The final follow-up visits for survival analysis were conducted on June 1, 2017. Informed consent was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Beijing Hospital.

Chemotherapy Regimens

The decision to treat a patient and the choice of the type and intensity of treatment were always left to the clinical judgment of the attending physician, who was blinded to the results of the ACA index. According to the intensity of chemotherapy, the regimen included (a) high intensity:R-CHOP-21 (375 mg/m² rituximab on day 0; 750 mg/m² cyclophosphamide on day 1; 50 mg/m² doxorubicin, 70 mg/m² epirubicin, or 40 mg liposomal doxorubicin, 40 mg on day 1; 1.4 mg/m² vincristine [capped at 2 mg per day] or 4 mg vindesine on day 1; and 100 mg prednisolone per day on days 1 to 5) every 3 weeks, (b) intermediate intensity:R-reduced intensity CHOP (R-riCHOP; 375 mg/m² rituximab on day 0; 750 mg/m² cyclophosphamide on day 1; 25–35 mg/m² doxorubicin, 35–50 mg/m² epirubicin, or 20–30 mg liposomal doxorubicin on day 1; 1.4 mg/m² vincristine [capped at 2 mg per day] or 4 mg vindesine on day 1; and 100 mg prednisolone per day on days 1 to 5) every 3 weeks, or (c) low intensity:R-miniCHOP (375 mg/m² rituximab on day 0; 400 mg/m² cyclophosphamide on day 1; 25 mg/m² doxorubicin, 35 mg/m² epirubicin, or 20 mg liposomal doxorubicin on day 1; 2 mg vindesine on day 1; and 40 mg/m² prednisolone per day on days 1 to 5) every 3 weeks or R-COP (375 mg/m² rituximab on day 0, 750 mg/m² cyclophosphamide on day 1, 1.4 mg/m² vincristine [capped at 2 mg per day] or 4 mg vindesine on day 1, and 100 mg prednisolone per day on days 1 to 5) every 3 weeks.

ACA Index

According to the research of Miura et al. [8], the ACA index comprises three risk factors: advanced age (>75 years), hypoalbuminemia (<3.7g/dL), and high burden of clinical comorbidities (Charlson Comorbidity Index [CCI] score ≥3). Based on this ACA index score, patients were categorized into "excellent" (0 points), "good" (1 point), "moderate" (2 points), and "poor" (3 points) groups. In order to verify the efficacy of ACA index in our cohort, we used the same cutoff values for age, hypoalbuminemia, and CCI scores in the present study.

Definitions and Assessments

The comorbidities at diagnosis were assessed based on the CCI scores [9]. The performance status was assessed based on the Eastern Cooperative Oncology Group (ECOG) and Karnofsky scale scores. The patients' activity ability was assessed based on activities of daily living (ADL) [10] and instrumental activities of daily living (IADL) scales [11]. Toxicities of therapy were rated according to the World Health Organization criteria [12]. Overall response rate (ORR) included complete remission (CR), complete remission unconfirmed (CRu), and partial remission (PR). Responses were assessed by the treating physicians after the end of treatment [13, 14]. After the fourth and eighth cycles, patients underwent disease reassessment by fluorodeoxyglucose positron emission tomography or computed tomography (CT), the choice of which depended on the economic status of the patients. During the first 2 years, clinical and biochemical follow-up was conducted every 3 months and thereafter every 6 months. A CT scan or ultrasonography was carried out every 3 months for the first 2 years of the follow-up period. Relapse or disease progression was defined according to the criteria of Cheson et al. [14]. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from diagnosis until progression, relapse, or death from any cause. Patients without PFS or OS events were censored to the last date with valid information for that end-point. Treatment-related mortality (TRM) was defined as death without evidence of disease relapse or progression.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney U test; categorical variables were compared using chi-square and Fisher's exact tests. Survival probabilities were estimated by means of the Kaplan-Meier method. Competing risk analyses were used to calculate the cumulative incidence of relapse and progression and TRM, using Gray's test to test for differences between the groups [15].

To refine the ACA index, hazard ratios for OS were estimated from univariate and multivariate Cox regression analyses. All factors with $p < .1$ in the univariate analysis were included in a multivariate regression, and $p < .05$ was considered to be statistically significant. The level of significance was set at $p < .05$. All reported p values were based on two-sided tests. Data analyses were primarily conducted with SPSS software (SPSS Inc., Chicago, IL), and the R software package (version 2.6.1; R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org) was used for competing risk analysis.

RESULTS

Patient Characteristics

Characteristics of the 99 patients are summarized in Table 1. Thirty-nine, 31, 26, and 3 patients were categorized into the ACA "excellent," "good," "moderate," and "poor" groups, respectively. Because there were only 3 patients in the "poor" group, we combined the "moderate" and "poor" groups to form the "moderate to poor" group. In the "moderate to poor" group, more patients showed high ECOG and low Karnofsky scores, were low on the ADL and IADL scales, and showed elevated lactate dehydrogenase levels and high-risk international prognostic index DLBCL. Most patients in the "excellent" group

Table 1. Patient characteristics

Characteristics	ACA "excellent" group (score 0, *n* = 39)	ACA "good" group (score 1, *n* = 31)	ACA "moderate to poor" group (score ≥2, *n* = 29)	*p* value
Sex, *n* (%)				
Male	23 (59.0)	18 (58.1)	14 (48.3)	.642
Female	16 (41.0)	13 (41.9)	15 (51.7)	
Median age at diagnosis, years (range)	70 (65–78)	73 (65–89)	83 (66–92)	<.001
ECOG performance score >1, *n* (%)	0 (0.0)	6 (19.4)	11 (37.9)	<.001
Karnofsky score <90, *n* (%)	4 (10.3)	8 (25.8)	13 (44.8)	.005
ADL score, *n* (%)				
6	39 (100.0)	27 (87.0)	20 (69.0)	<.001
4–5	0 (0.0)	2 (6.5)	5 (17.2)	
≤3	0 (0.0)	2 (6.5)	4 (13.8)	
IADL score, *n* (%)				
8	39 (100.0)	24 (77.4)	15 (51.7)	<.001
6–7	0 (0.0)	5 (16.1)	9 (31.0)	
≤5	0 (0.0)	2 (6.5)	5 (17.3)	
CCI score, ≥3, *n* (%)	0 (0.0)	3 (9,7)	12 (41.4)	<.001
Ann Arbor stage, *n* (%)				
Stage I–II	19 (48.7)	9 (29.0)	7 (24.1)	.075
Stage III–IV	20 (51.3)	22 (71.0)	22 (75.9)	
Non-GCB DLBCL	28 (71.8)	20 (64.5)	21 (75.0)	.211
More than one extranodal site, *n* (%)	20 (51.3)	13 (41.9)	19 (65.5)	.184
Bone marrow involvement, *n* (%)	4 (10.3)	3 (9.7)	6 (20.7)	.399
Elevated LDH, *n* (%)	14 (35.9)	14 (45.2)	19 (65.5)	.051
Serum albumin<3.7 g/dL, *n* (%)	0 (0.0)	21 (67.7)	23 (79.3)	<.001
IPI risk group, n (%)				
Low (0–1)	15 (38.5)	2 (6.4)	4 (13.9)	<.001
Intermediate-1 (2)	5 (12.8)	12 (38.7)	3 (10.3)	
Intermediate-2 (3)	10 (25.6)	10 (32.3)	3 (10.3)	
High (4–5)	9 (23.1)	7 (22.6)	19 (65.5)	
Intensity of chemotherapy regimen administered, *n* (%)				
High	27 (69.2)	9 (29.0)	2 (6.9)	<.001
Intermediate	9 (23.1)	12 (38.7)	6 (20.7)	
Low	3 (7.7)	10 (32.3)	21 (72.4)	
Median duration of follow-up, days (range)	596 (82–3,683)	689 (12–2,984)	288 (6–1,800)	.029

Statistical significance was set at *p* < .05.
Abbreviations: ACA index, Age, Comorbidities, and Albumin index; ADL, activities of daily living; CCI, Charlson Comorbidity Index; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell-like; IADL, instrumental activities of daily living; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

received high-intensity chemotherapy regimens, while most patients in the "moderate to poor" group received low-intensity chemotherapy regimens.

Toxicities and TRM

The grade ≥3 toxicities observed are summarized in supplemental online Table 1. Hematologic toxicities were the most common toxicity noted after chemotherapy, followed by infectious, cardiovascular, and gastrointestinal toxicities. The ratios of grade ≥3 infectious toxicities were significantly higher in the ACA "moderate to poor" group, and the other toxicities were comparable among the three groups.

Eight patients died of TRM. The most common cause of TRM was infection (*n* = 4), followed by myocardial infarction (*n* = 1), malignant ventricular arrhythmia (*n* = 1), stroke (*n* = 1), and second malignancy (*n* = 1). The 2-year cumulative incidence of TRM was significantly higher in the ACA "moderate to poor" group (22.1%) compared with that of the ACA "good" (0.0%) and "excellent" groups (0.0%; Fig. 1A).

Response and Relapse

The rates of CR, CRu, PR, and ORR were 55.6%, 4.0%, 20.2%, and 79.8%, respectively, in the total population. The ORR in the ACA "excellent" group was the highest (97.5%), but the ORRs
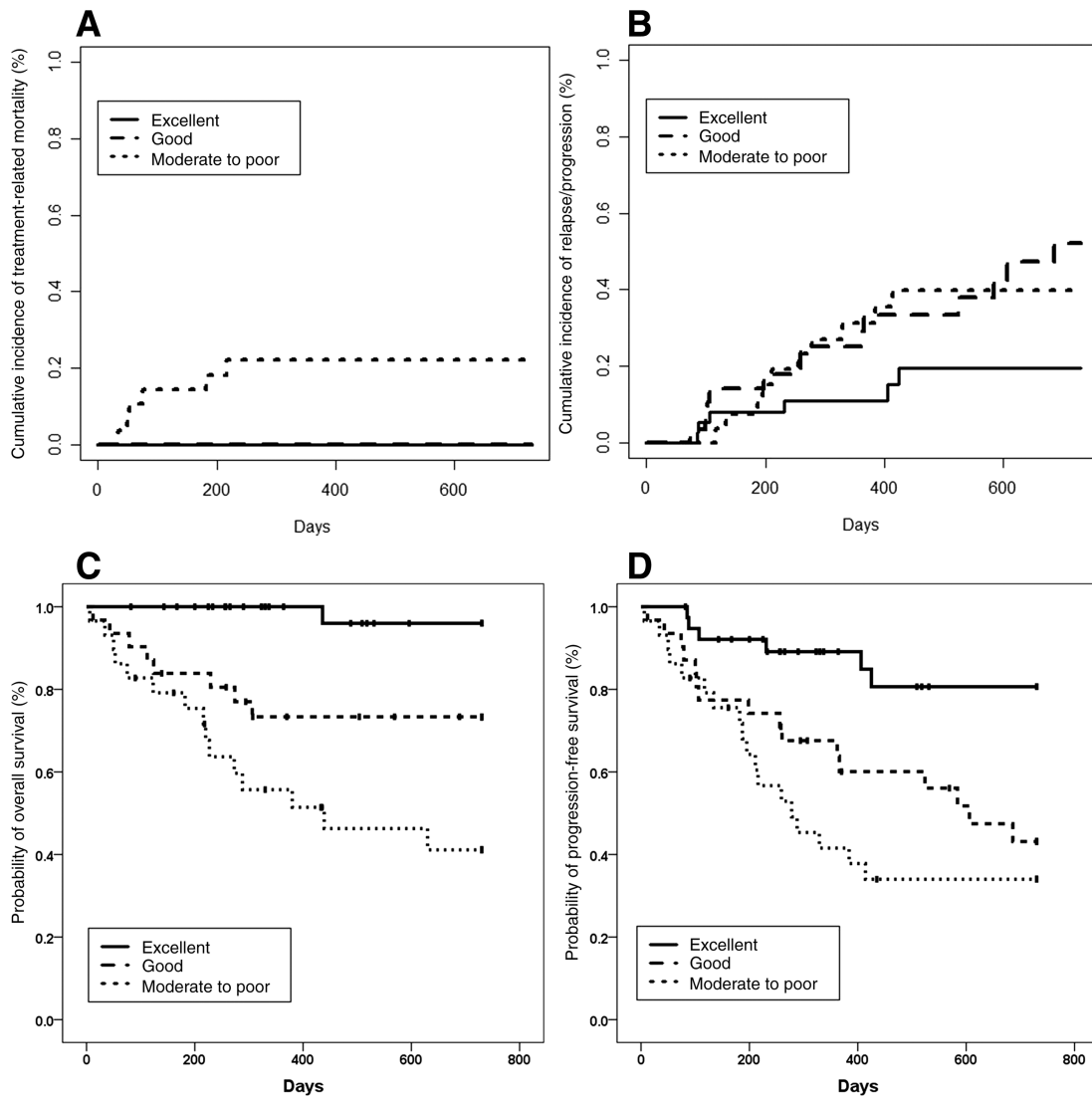
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Figure 1. Outcomes for patients grouped according to the Age, Comorbidities, and Albumin index. **(A)**: Treatment-related mortality. **(B)**: Relapse or progression. **(C)**: Overall survival. **(D)**: Progression-free survival.

Table 2. Response to treatment

Response	Total, n (%)	ACA "excellent" group (score 0, n = 39), n (%)	ACA "good" group (score 1, n = 31), n (%)	ACA "moderate to poor" group (score ≥2, n = 29), n (%)
CR	55 (55.6)	31 (79.5)	14 (45.2)	10 (34.5)
CRu	4 (4.0)	1 (2.6)	2 (6.5)	1 (3.4)
PR	20 (20.2)	6 (15.4)	7 (22.6)	7 (24.1)
ORR for CR + CRu + PR	79 (79.8)	38 (97.5)	23 (74.3)[a]	18 (62.0)[b]

Response	Total, n (%)	IACA low-risk group (n = 39), n (%)	IACA intermediate-risk group (n = 44), n (%)	IACA high-risk group (n = 16), n (%)
CR	55 (55.6)	31 (79.5)	22 (50.0)	2 (12.5)
CRu	4 (4.0)	1 (2.6)	3 (6.8)	0 (0.0)
PR	20 (20.2)	6 (15.4)	10 (22.7)	4 (25.0)
ORR for CR + CRu + PR	79 (79.8)	38 (97.5)	35 (79.5)[c]	6 (37.5)[d]

[a]Compared with ACA "excellent" group, $p = .008$.
[b]Compared with ACA "good" group, $p = .313$.
[c]Compared with low-risk group, $p = .016$.
[d]Compared with intermediate-risk group, $p = .002$.
Abbreviations: ACA, Age, Comorbidities, and Albumin index; CR, complete remission; CRu, unconfirmed complete response; IACA index, IADL, Age, Comorbidities, and Albumin index; IADL, instrumental activities of daily living; ORR, overall response rate; PR, partial response.

CME

Table 3. Univariate and multivariate analyses of variables for overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
ECOG score						
<2	1.00		**<.001**			
≥2	5.28	1.86–14.99				
Karnofsky score						
≥90	1.00		**.001**			
<90	3.77	1.69–8.40				
ADL scale						
6	1.00					
4–5	3.84	1.28–11.55	**.017**			
≤3	5.05	1.68–15.16	**.004**			
IADL scale						
8	1.00			1.00		
6–7	6.18	2.46–15.57	**<.001**	2.88	1.10–7.50	**.031**
≤5	8.11	2.80–23.56	**<.001**	3.85	1.29–11.52	**.016**
Ann Arbor stage						
I to II	1.00		.051			
III to IV	2.92	0.99–8.54				
Bone marrow involvement						
None	1.00		**.031**			
Yes	2.77	1.10–6.98				
LDH						
Normal	1.00		**.004**			
Elevated	3.90	1.55–9.84				
ACA index						
"Excellent"	1.00			1.00		
"Good"	10.76	1.35–86.01	**.025**	7.59	0.92–62.62	.060
"Moderate to poor"	26.68	3.52–202.23	**.001**	15.20	1.87–123.47	**.001**

Bold font indicates statistical significance (*p* < .05).

Abbreviations: ACA index, Age, Comorbidities, and Albumin index; ADL, activities of daily living; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase.

were comparable between the ACA "good" and "moderate to poor" groups (Table 2). The 2-year cumulative incidence of relapse was lowest in the ACA "excellent" group (Fig. 1B).

OS and PFS

The 2-year probabilities of OS were 96.0% and 73.3% in the ACA "excellent and "good" groups, respectively (*p* = .005), which were both significantly higher than that of the ACA "moderate to poor" group (41.1%, Fig. 1C). The 2-year probability of PFS was the highest in the ACA "excellent" group (80.6%), but the 2-year probabilities of PFS was comparable between the ACA "good" group (43.1%) and "moderate to poor" group (34.0%, *p* = .264; Fig. 1D).

Refinement of the ACA Index

We constructed a Cox proportional hazards model with the following variables: ECOG score (<2 vs. ≥2), Karnofsky performance status (90–100 vs. <90), ADL scale (6 vs. 5–4 vs. 3), IADL scale (8 vs. 6–7 vs. ≤5), Ann Arbor stage (grades I–II vs. grades III–IV), bone marrow involvement (yes vs. no), lactate dehydrogenase levels (normal vs. elevated), extranodal involvement

(>1 vs. 0–1), and ACA index ("excellent" vs. "good" vs. "moderate to poor").

In the univariate analysis, ECOG score, Karnofsky performance status, ADL scale, IADL scale, Ann Arbor stage, bone marrow involvement, lactate dehydrogenase levels, and ACA index were the potential predictors of OS. Finally, the multivariable model identified two independent predictors of OS: IADL scale and ACA index (Table 3). IADL scale score 6 to 7 and the ACA "good" group were assigned 1 point and IADL scale ≤5 and the ACA "moderate to poor" group were assigned 2 points. Thus, we created a three-category system, the IADL ACA index (IACA index): low risk, score 0 (*n* = 39); intermediate risk, score 1 to 2 (*n* = 44); and high risk, score 3 to 4 (*n* = 16; supplemental online Table 2).

Validation of the IACA Index in the Present Cohort

The ORR of the low-risk group was higher than that of the intermediate-risk group (97.4% vs. 79.5%, *p* = .016), and the ORR of the intermediate-risk group was higher than that of the high-risk group (37.5%, *p* = .002; Table 2). The 2-year cumulative incidence of TRM was the highest in the high-risk group
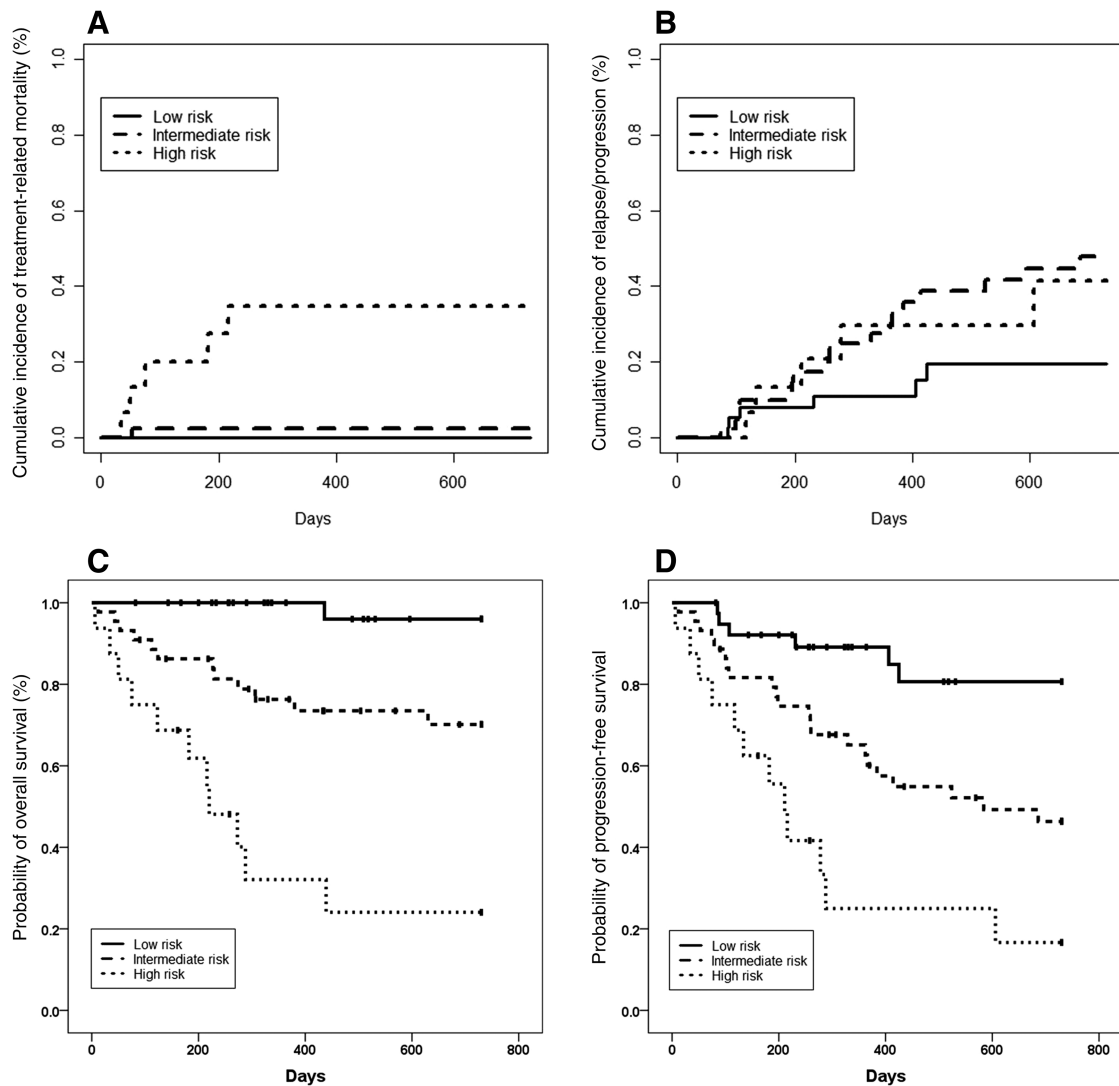
Figure 2. Outcomes for patients grouped according to the instrumental activities of daily living, Age, Comorbidities, and Albumin index. **(A)**: Treatment-related mortality. **(B)**: Relapse or progression. **(C)**: Overall survival. **(D)**: Progression-free survival.

(Fig. 2A), and the 2-year cumulative incidence of relapse was the lowest in the low-risk group (Fig. 2B).

The 2-year probabilities of OS were 96.0% and 70.1% in the low-risk and intermediate-risk groups, respectively ($p = .003$), which were both significantly higher than that of the high-risk group (24.1%, Fig. 2C). The 2-year probabilities of PFS were 80.6% and 46.4% in the low-risk and intermediate-risk groups, respectively ($p = .005$), which were both significantly higher than that of the high-risk group (16.7%, Fig. 2D).

Clinical Outcomes According to the Other CGA System

According to the CGA system of Tucci et al. [16], patients were classified as "fit" ($n = 49$), "unfit" ($n = 14$), and "frail" ($n = 36$) based on age, ADL/IADL, and the Cumulative Illness Rating Score for Geriatrics (CIRS-G). The 2-year probabilities of OS (90.8%) and PFS (72.9%) were the highest in the "fit" group, but survival was comparable between the "unfit" (OS: 43.0%; PFS: 32.5%) and "frail" groups (OS: 58.5%; PFS: 37.3%; supplemental online Fig. 1A and 1B). We found that the IACA index resulted in the reclassification of patients in the "fit," "unfit," and "frail" classifications (supplemental online Fig. 2).

DISCUSSION

In our study, we first observed that the ACA index could partially predict the clinical outcomes in an independent Chinese cohort. Combining the features of ACA index and IADL scale, we propose a new and more effective index (IACA index) for elderly patients with DLBCL that can predict both ORR and survival.

The ORR was 79.8% in the present study, which was similar to the results of Coiffier et al. (82%) [17], Pfreundschuh et al. (81%–84%) [18], and Habermann et al. (77%) [19]. These results supported that chemotherapy plus rituximab is useful for elderly patients with DLBCL.

IADL skills are those required to maintain independence in the community [11]. The evaluation of IADL skills, in particular, adds substantially to the functional information provided by ECOG and Karnofsky performance status values [20], and patients over the age of 80 years are more likely to require assistance in IADL skills [21]. The importance of the IADL scale has been observed in the CGA of patients with acute myeloid leukemia [22], multiple myeloma [23], and chronic lymphoblastic leukemia [24], and it is also one of the important components of the CGA in patients with DLBCL [25].

CGA is an effective method to identify elderly patients with DLBCL who can benefit from a curative approach with anthracycline-containing immunochemotherapy. In the study of Tucci et al. [25], patients were classified as "fit" and "unfit." The "fit" patients received curative treatment, and their response rate and median survival were significantly better than those of "unfit" patients. Other authors have also reported that CGA (including age, ADL/IADL, and CIRS-G) is a valid tool to prospectively identify frail subjects among elderly patients with DLBCL [26] and also to identify patients who can benefit from a curative approach [16]. In addition, the chemo-immunotherapy adjustments based on a CGA are associated with manageable toxicity and excellent outcomes [27]. Combining the use of the IADL and ACA indexes (including age and comorbidity score according to CCI), our IACA index is a relative integral CGA system [20]. We observed that the IACA index could predict response rate, OS, and PFS in elderly patients with DLBCL. Particularly, ORR and survival were both significantly better in the intermediate-risk group than in the high-risk group. Thus, it is suggested that IACA index is an effective method for CGA in DLBCL.

The critical difference between the IACA index and the previous CGA system [16, 25–27] was the scores for comorbidity evaluation. CCI in the IACA index, which may be easier and quicker to apply than CIRS-G [28], was also suggested to be useful in CGA for patients with other hematologic malignances [29, 30]. Some authors suggested that CIRS-G provides a more complete assessment of comorbidity and, therefore, may be more suitable to measure comorbidity in older people [31, 32]. However, when we used the CGA system of Tucci et al. [16] in the present study, we observed that although survival was best in the "fit" group, it was comparable between the "unfit" and "frail" groups, and this result is in accordance with previous studies [16, 27]. Thus, the IACA index may be more suitable for elderly patients with DLBCL. However, as only a few studies have compared the efficacy of CCI and CIRS-G directly in CGA, we could not derive substantial conclusions regarding the superiority of CCI over CIRS-G in CGA for DLBCL.

There were several limitations in this study. First, this is a retrospective study with a relatively small number of elderly patients with DLBCL, which could have influenced the accuracy of our findings. In addition, only three patients were categorized as being "poor" in the ACA index, which could have influenced our validation of the index. Lastly, CCI is not as extensively used in the U.S. as in other countries, which may limit the applicability of IACA index in elderly patients with DLBCL. Thus, we suggest that elderly patients with DLBCL are worthy of receiving CCI evaluation.

Conclusion

We observed that that ACA index can partially predict clinical outcomes of elderly patients with DLBCL in China. Based on this index, we propose the use of the IACA index as an effective tool for CGA in DLBCL. Additional large, prospective studies can further identify and compare the validity of the IACA index and other CGA methods among elderly patients with DLBCL. In addition, we should identify the efficacy and safety of IACA-index-directed therapy in elderly patients with DLBCL.

Author Contributions

Conception/design: Hui Liu, Chun-Li Zhang
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Data analysis and interpretation: Chun-Li Zhang
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