Article published online: 2021-06-03

Original Article

Serum Albumin Predicts Survival in Indian Adult Diffuse Large B cell Lymphoma Patients in the Rituximab Era

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Abstract

Objective: The present study was done to evaluate the prognostic impact of the National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) and serum albumin levels in the treatment outcome of Indian diffuse large B-cell lymphoma (DLBCL) patients in the rituximab era. **Patients and Methods:** We retrospectively analyzed the data (2013–2016) of 135 newly diagnosed DLBCL cases ≥18 years of age. All patients received Rituximab-Cyclophosphamide, Adriamycin, Vincristine, Prednisone (R-CHOP) chemotherapy. The analysis was carried out to assess the overall survival (OS) and progression-free survival (PFS) and the prognostic factors predicting the outcome. **Results:** Of the 135 patients in the study, 89 (65.9%) had B-symptoms, 20 (14.8%) had bulky disease, 79 (58.5%) had advanced disease (Stage III and IV), and 29 (21.5%) had primary extranodal involvement. Serum albumin ≤3.5 g% was present in 71 (52.6%) patients. About 74 (54.8%) cases were risk stratified to NCCN-IPI high-intermediate-risk group, while 18 (13.3%) patients were categorized into high-risk group. The median PFS and OS of our study cohort were 19 months (95% confidence interval [CI] = 2.59–35.4) and 38 months (95% CI = 9.02–55.68), respectively. Serum albumin ≤3.5 g/dl was significantly associated with poor OS (hazard ratio [HR] = 3.99, 95% CI = 2.25–7.07, $P < 0.001$) and PFS (HR = 3.71, 95% CI = 2.20–6.26, $P < 0.002$). Similarly, low NCCN-IPI (<4) was significantly associated with improved OS (HR = 0.21, 95% CI = 0.09–0.47, $P < 0.005$) and PFS (HR = 0.19, 95% CI = 0.09–0.41, $P < 0.001$), respectively. These two factors (serum albumin and NCCN-IPI) retained their prognostic significance with respect to OS and PFS in the multivariate analysis. **Conclusion:** The NCCN-IPI prognostic model and serum albumin levels have independent prognostic significance in Indian DLBCL patients. Serum albumin is a readily available, easy to standardize, and cheap investigation requiring no specialized expertise and holds promise for being incorporated in future DLBCL prognostic risk models.

Keywords: *Albumin, diffuse large B-cell lymphoma, National Comprehensive Cancer Network-International Prognostic Index, prognosis*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) in adults constituting around 20% of all NHL cases.[1] It is a highly heterogeneous disease with respect to tumor biology, clinical features, response to treatment, and outcome. As a result, there has always been a need for an accurate-risk stratification system that can easily differentiate the "low-risk" from the "high-risk" disease group so that the treatment can be tailored accordingly.

For around two decades, the International Prognostic Index (IPI) derived from five prognostic factors, such as age, Ann Arbor tumor stage, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, and number of extranodal sites involved, holds its prognostic significance in discriminating patients with aggressive lymphomas into four discrete outcome groups with a 5-year overall survival (OS) ranging from 26% to 73% even in the postrituximab era.[2,3] However, one potential limitation to the use of the original IPI in patients receiving rituximab is that the difference in outcomes between patients in different IPI-risk groups is relatively small. Several prognostic models have been developed since then to improvise the IPI prognostic model using the same prognostic factors in a more detailed way to provide better discrimination between risk groups.[4] One such prognostic model is the National

How to cite this article: Gupta A, Mishra P, Nityanand S. Serum albumin predicts survival in indian adult diffuse large B cell lymphoma patients in the rituximab era. Indian J Med Paediatr Oncol 2019;40:232-9.

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_96_18

Quick Response Code:

Comprehensive Cancer Network-IPI (NCCN-IPI) that provided better discrimination between risk groups with OS ranging from 38% to 96%.[5]

Recently, several attempts have been made to more accurately segregate high risk from low-risk patients using various molecular and genetic markers (e.g., germinal center B-cell type vs. activated B-cell-like subtypes and various somatic mutations).[6-9] However, their widespread use in clinical practice is still limited due to the lack of standardized protocols, sophisticated laboratories to perform these tests, and their prohibitive cost, especially in the developing world. As a result, there is an unmet need of identifying readily and universally available as well as affordable parameters that can help in predicting disease outcome.

Serum albumin may be one such parameter as several studies have shown its correlation with treatment outcome in various hematological malignancies.[10-17] It is a surrogate marker of disease burden in cancers, comorbidity, and nutritional status.[18-21] Notably, serum albumin was found to be statistically significant in the univariate analysis in the IPI prognostic model. However, since its values were available in an insufficient number of patients, it was excluded from the step-down regression model.[2]

Hence, the aims of the present study were to evaluate the prognostic impact of NCCN-IPI and serum albumin levels in the treatment outcome (OS and progression-free survival [PFS]) of Indian DLBCL patients in the rituximab era.

Patients and Methods

Patients

The present study is a single-institutional study carried out in a tertiary care medical university center of North India. A retrospective chart review of medical records of patients with ages >18 years with a confirmed diagnosis of DLBCL and treated with combination immunotherapy (R-CHOP) in the department of hematology from January 2013 to December 2016 was carried out. In all cases, the diagnosis of DLBCL was established by tissue biopsy and classified according to the WHO classification of tumors.[22] The following clinical and laboratory data were collected from medical files: demographic profile, clinical presentation, ECOG performance status, serum LDH level, Ann Arbor stage, number of extranodal sites involved, complete blood count, histopathological report with immunohistochemistry, Ki-67 index, and serum albumin level. The revised IPI (R-IPI) scores were calculated based on age, serum LDH, ECOG performance status, number of extranodal sites at diagnosis, and Ann Arbor stage of the disease. Low serum albumin was defined as <3.5 g/dl, while serum albumin ≥3.5 g/dl was labeled as normal. The exclusion criteria included patients with transformed lymphoma, incomplete clinical data, relapse/refractory cases, primary central nervous system lymphoma, and primary mediastinal B-cell lymphoma and patients who received CHOP chemotherapy only. Informed consent was taken from all the study participants for participation in the study and before start of chemotherapy. The study was approved by the Institutional Ethics Committee.

Treatment data

All the patients in the study cohort received R-CHOP chemotherapy. The date of start and completion of R-CHOP chemotherapy cycles were recorded along with the total number of cycles that were received by each patient. Interim treatment response evaluation done by whole-body ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) between 3 and 4 cycles of R-CHOP was recorded and classified as per Lugano response assessment criteria.[23] End-of-treatment (after 6–8 cycles) PET-CT evaluation data along with 3 monthly follow-up data were systematically recorded. Other recorded data included whether the patient received the intrathecal therapy and/or radiation therapy along with its indication of use.

Statistical analysis

Descriptive statistics were obtained using mean with standard deviation or median with range and categorical variables were represented by frequencies with corresponding percentages. Differences in the distribution of individual parameters among subsets of patients were analyzed using Fisher's exact test or the Chi-square test for categorical variables and the Mann–Whitney *U*-test for continuous variables. OS was defined as date of diagnosis to date of death or date of last follow-up for those censored. PFS was defined as date of diagnosis to date of relapse, progression, or death. Survival curves for OS and PFS were drawn employing Kaplan–Meier method and were compared using log-rank test. Cox proportional hazards regression model was applied to consider each potential prognostic factor in univariate and multivariate analyses. Adjusted hazard ratios (HRs) were estimated with 95% confidence intervals (CIs). Bivariate associations between serum albumin and other variables were examined using Spearman's correlation coefficient. The data were analyzed using IBM SPSS statistics for windows version 21.0 (Armonk, NY). $P < 0.05$ was considered as statistically significant.

Results

Of the total 172 patients who were diagnosed as DLBCL at our center during the study period, 135 patients were included in the study. The reasons for excluding 37 patients from the study were as follows: five patients defaulted therapy due to the lack of finances for the treatment, eight patients received only CHOP chemotherapy, and 24 patients did not seek treatment at our center.

Baseline characteristics

The demographic and disease characteristics of these patients are shown in Table 1. The median age at presentation was 58 years (range: 18–82 years) with a preponderance of male (M:F = 2.5:1) patients. The mean duration of symptoms before being diagnosed as DLBCL at our center was 56.4 ± 42.3 days. Of the eligible 135 patients in the study, 89 (65.9%) had B-symptoms, 20 (14.8%) had bulky disease, 79 (58.5%) had advanced disease (Stage III and IV) at presentation, and 29 (21.5%) had primary extranodal involvement. Serum albumin <3.5 g% was present in 71 (52.6%), and high NCCN-IPI score (≥4) was present in 92 (68.1%) cases.

Treatment and response evaluation

The median number of R-CHOP chemotherapy cycles received by our study cohort was 6 (range: 1–8). About 30 (22.2%) patients received <6 chemotherapy cycles (20 patients showed progression/nonresponse of disease on interim PET-CT evaluation and hence shifted to salvage chemotherapy, while 10 patients had toxic deaths due to febrile neutropenia). On interim PET-CT evaluation (after 3–4 cycles of R-CHOP chemotherapy) for assessing the response to chemotherapy, 70 (51.8%) patients achieved complete response (CR), 38 (28.1%) showed partial response (PR), and 20 (14.8%) showed progression/nonresponse to the therapy. In 8 (5.9%) patients, the response could not be assessed as they had toxic deaths due to febrile neutropenia. The end-of-treatment (post 6–8 cycles of R-CHOP chemotherapy) PET-CT evaluation could be done in 105 patients, the details of which are shown in Table 2. Of the 97 patients who showed CR/PR at the end-of-treatment PET-CT, 33 (34%) patients relapsed on follow-up.

Survival

The median follow-up of our study group was 18 months (1–46 months). The median PFS and OS of our study cohort were 19 months (95% CI = 2.59–35.4) and 38 months (95% CI = 9.02–55.68), respectively [Figure 1].

Prognostic factors

Univariate analysis of various potential prognostic factors showed serum albumin and NCCN-IPI to be associated with OS and PFS. Serum albumin ≤3.5 g/dl was significantly associated with poor OS (HR = 3.99, 95% CI = 2.25–7.07), $P < 0.001$, and PFS (HR = 3.71, 95% CI = 2.20–6.26), $P < 0.002$ [Figure 2]. Similarly, low NCCN-IPI (<4) was significantly associated with improved OS (HR = 0.21, 95% CI = 0.09–0.47), $P < 0.005$, and PFS (HR = 0.19, 95% CI = 0.09–0.41), $P < 0.001$, respectively [Table 3 and Figure 3]. These two factors (serum albumin and NCCN-IPI) retained their prognostic significance with respect to OS and PFS in the multivariate analysis as shown in Table 4. Of the 74 patients in the high intermediate risk (NCCN-IPI: 4–5) and 18 patients in the high risk (NCCN-IPI: ≥6), stratification of patients based on serum albumin (≤3.5 g/dl or >3.5 g/dl) further identified the subset of patients with significantly poor OS and PFS as shown in Table 5 and Figure 4.

There was significant correlation found between the serum albumin and ECOG performance status (Spearman's correlation coefficient: −0.32, $P = 0.001$) as well as NCCN-IPI risk groups (Spearman's correlation coefficient: −0.194, $P = 0.02$). Similarly, a significant correlation was found between

Table 1: Clinical and laboratory characteristics in patients with diffuse large B-cell lymphoma

Characteristics	Values
Age (year), median (range)	58 (18-82)
Male:female (ratio)	2.5:1
Disease stage, *n* (%)	
I	4 (3)
II	52 (38.4)
III	35 (26)
IV	44 (32.6)
Ki-67 proliferation index (%), mean±SD	74.4±15.25
B-symptoms, *n* (%)	89 (65.9)
Bulky disease (>7.5 cm), *n* (%)	20 (14.8)
Extranodal involvement, *n* (%)	55 (40.7)
Primary extranodal involvement, *n* (%)	29 (21.5)
ECOG performance status, *n* (%)	
0-1	44 (32.6)
2-4	91 (67.4)
Elevated LDH, *n* (%)	117 (86.6)
NCCN-IPI (number of risk factors)	
Low risk (0)	0
Low intermediate (1, 2)	43 (31.8)
High intermediate (3, 4, 5)	74 (54.8)
High	18 (13.3)
Serum albumin (g/dl)	
Mean±SD	3.6±0.59
>3.5 g/dl	64 (47.4)
≤3.5 g/dl	71 (52.6)
Hemoglobin (g/dl), mean±SD	10.35±2.53
ALC (/μl), mean±SD	2372.86±2124.92
Mean duration of symptoms, days±SD	56.46±42.31

SD – Standard deviation; ALC – Absolute lymphocyte count; LDH – Lactate dehydrogenase; ECOG – Eastern Cooperative Oncology Group; NCCN – National Comprehensive Cancer Network; IPI – International Prognostic Index

Table 2: Chemotherapy response assessment by positron emission tomography–computed tomography

Response	Interim PET-CT (*n*=127), *n* (%)	End-of-treatment PET-CT (*n*=105), *n* (%)
Complete response	70 (51.8)	90 (66.6)
Partial response	37 (27.4)	7 (5.1)
Progression/nonresponse	20 (14.8)	8 (5.9)

PET – Positron emission tomography; CT – Computed tomography

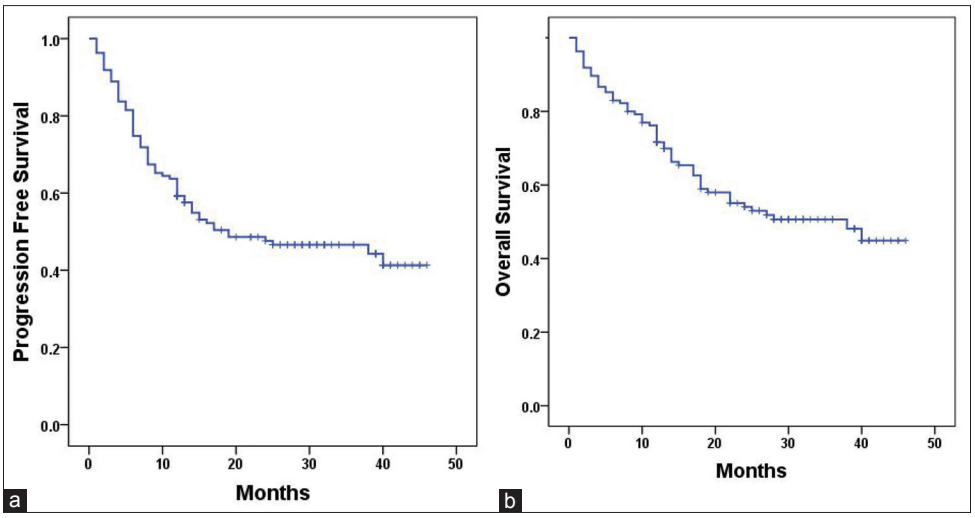

Figure 1: (a) Progression-free survival and (b) overall survival

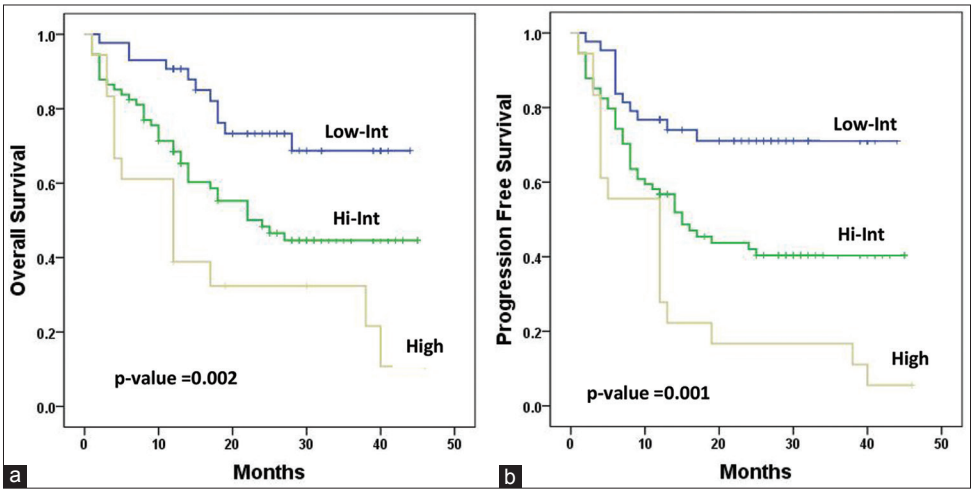

Figure 2: (a) Overall survival stratified according to the National Comprehensive Cancer Network-International Prognostic Index and (b) progression-free survival stratified according to the National Comprehensive Cancer Network-International Prognostic Index

Table 3: Univariate analysis for overall survival and progression-free survival

Variable	Overall survival		Progression-free survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	1.09 (0.62-1.91)	0.75	1.14 (0.67-1.93)	0.62
Serum albumin	3.99 (2.25-7.07)	0.001	3.71 (2.20-6.26)	0.002
NCCN-IPI	2.79 (1.45-5.35)	0.002	2.88 (1.550-5.37)	0.001
Extranodal disease	0.74 (0.41-1.35)	0.34	0.77 (0.44-1.35)	0.37
Bulky disease	0.90 (0.45-1.78)	0.77	1.19 (0.65-2.18)	0.56
B-symptoms	1.15 (0.67-1.96)	0.60	1.31 (0.79-2.19)	0.28
Absolute lymphocyte count	1.36 (0.82-2.26)	0.22	1.44 (0.90-2.31)	0.12
CNS disease at presentation	1.99 (0.72-5.51)	0.18	1.73 (0.63-4.77)	0.28

CI – Confidence interval; HR – Hazard ratio; NCCN – National Comprehensive Cancer Network; IPI – International prognostic index; CNS – Central nervous system

serum albumin and body mass index (BMI) (Spearman's correlation coefficient: 0.26, $P = 0.03$). However, no significant correlation was found between the age and serum albumin (Spearman's correlation coefficient: −0.069, $P = 0.429$).

Discussion

Our results suggest that serum albumin is an independent prognostic marker for the outcome in DLBCL patients in the rituximab era, affecting both the PFS and OS. We observed a significant correlation of serum albumin levels

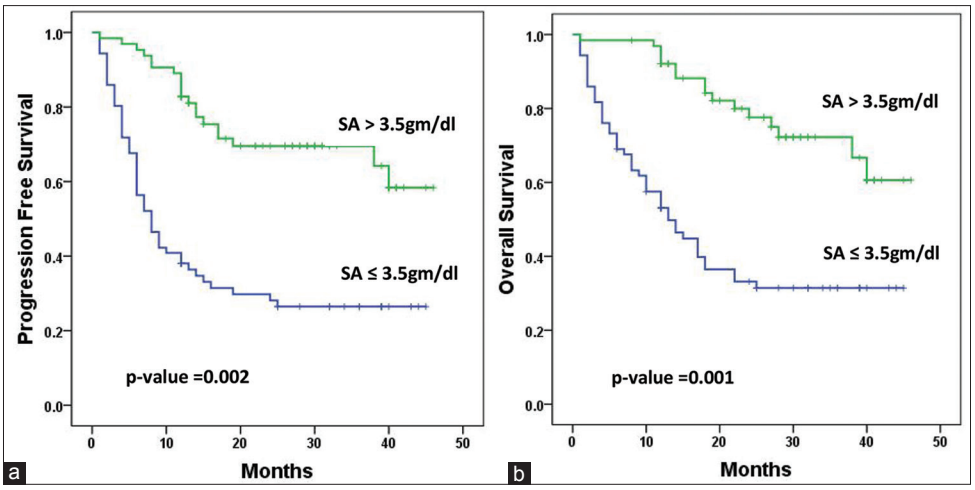

Figure 3: (a) Progression-free survival stratified according to serum albumin and (b) overall survival stratified according to serum albumin

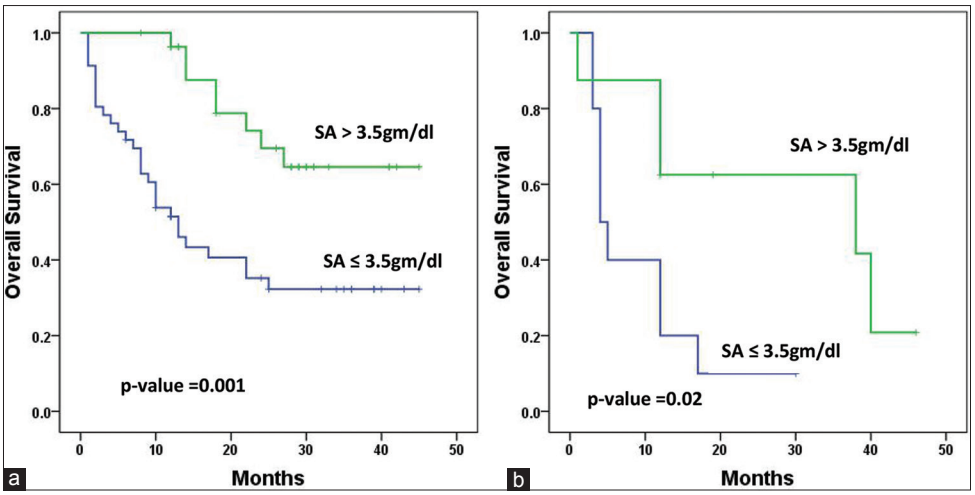

Figure 4: (a) Overall survival of high-intermediate-risk patients based on serum albumin and (b) overall survival of high-risk patients based on serum albumin

Table 4: Multivariate analysis for overall survival and progression-free survival

Variable	Overall survival		Progression-free survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Serum albumin	3.56 (1.99-6.34)	0.001	3.28 (1.93-5.55)	0.000
NCCN-IPI	2.25 (1.16-4.35)	0.016	2.31 (1.23-4.34)	0.009

CI – Confidence interval; HR – Hazard ratio; NCCN – National Comprehensive Cancer Network; IPI – International Prognostic Index

with perfomance status (PS)- and NCCN-IPI-risk groups, thereby suggesting that low serum albumin is a surrogate marker of advanced disease. It helped in identifying a subset of patients within the NCCN-IPI high-intermediate-risk and high-risk groups that had the worst survival. Further serum albumin levels also correlated significantly with the patient's baseline nutritional status (as measured by BMI), thereby suggesting that albumin levels are not only influenced solely by the disease process but also by the patient's baseline nutritional status.

The prognostic value of serum albumin in DLBCL patients has recently been highlighted in few studies.[24-30] Ochi *et al.* in their retrospective study of 391 DLBCL patients reported serum albumin to be significantly associated with OS (HR = 2.73, 95% CI = 1.65–4.51, $P < 0.001$).[24] Similarly, Melchardt *et al.* in their cohort of 499 DLBCL patients suggested that serum albumin and β_2-microglobulin (albumin HR: 1.97, 95% CI = 1.12–3.47, $P = 0.018$; β_2-microglobulin HR: 2.16, 95% CI = 1.16–3.99, $P = 0.014$) were independent prognostic factors affecting survival and proposed for revised NCCN-IPI incorporating these variables, especially in elderly (>60 years) DLBCL patients.[25] Our study also demonstrated similar results with a significant association of serum albumin with OS (HR: 3.56, 95% CI = 1.99–6.34; $P = 0.001$) and PFS (HR: 3.28, 95% CI = 1.93–5.55; $P = 0.000$).

Although NCCN-IPI prognostic model is more sensitive than the R-IPI in identifying high-risk DLBCL cases from low risk, its accuracy may be improved further by the addition of other robust pretreatment variables such

Table 5: Overall survival and progression-free survival of high-intermediate/high-risk patients based on serum albumin

NCCN-IPI risk group	Serum albumin	Overall survival		Progression-free survival	
		Mean survival, 95% CI (months)	*P*	Mean survival, 95% CI (months)	*P*
High intermediate (*n*=74) (g/dl)	>3.5	35.76±2.68 (30.50-41.03)	0.001	17.12±2.61 (11.99-22.25)	0.002
	≤3.5	20.54±2.74 (15.16-25.91)		33.63±3.07 (27.61-39.65)	
High (*n*=18) (g/dl)	>3.5	28.95±5.88 (17.41-40.49)	0.02	21.75±5.55 (10.85-32.64)	0.019
	≤3.5	9.4±2.61 (4.27-14.52)		7.0±1.71 (3.63-10.37)	

CI – Confidence interval; NCCN – National Comprehensive Cancer Network; IPI – International prognostic index

as serum albumin, β_2-microglobulin, and tumor biology (germinal center vs. activated B-cell type). NCCN-IPI proposed by Zhou *et al*. did not analyze important laboratory parameters (including serum albumin) except LDH while assigning risk groups to patients with *de novo* DLBCL.[5] Dalia *et al*. demonstrated hazard index of death of patients with serum albumin ≥3.7 g/dL was 26% (95% CI = 13–53) of the hazard for those patients who had serum albumin <3.7 g/dL when controlling for the R-IPI.[26] Bairey *et al*. in their cohort of 157 adult patients reported that 5-year OS of patients with a high NCCN-IPI and albumin <3.5 g/dl was 29.2% compared with 60% in patients with albumin >3.5 g/dl (*P* = 0.022).[27] Similar results were demonstrated in the present study. The relevance of serum albumin to prognosis in DLBCL has also been reported in Indian studies.[28,29] Prakash *et al*. reported serum albumin <4.0 g/dl to be an independent prognostic marker in DLBCL treatment outcome.[28] However, majority of patients in this study were treated with CHOP chemotherapy rather than R-CHOP, and these results may not be extrapolated to rituximab era.[29] Interestingly, Ngo *et al*. reported that serum albumin was an independent prognostic marker in patients of DLBCL treated on CHOP chemotherapy, while it lost its prognostic significance when their study cohort received R-CHOP chemotherapy.[30] However, these results were not confirmed by any large prospective multicenter studies.

The adverse impact of serum albumin on prognosis has also been documented in several other hematological malignancies such as HL, myelodysplastic syndrome, peripheral T-cell lymphoma, multiple myeloma, and splenic marginal zone lymphoma.[10-17] However, the exact mechanism(s) by which serum albumin is associated with poor prognosis is still unknown. Putative mechanisms that have been proposed for low serum albumin in advanced disease include the role of systemic inflammatory response to tumor leading to increased cytokine release which in turn is associated with increased weight loss, an elevated resting energy expenditure, loss of lean body tissue, and functional decline.[31,32] Thus, this process often exacerbates the preexisting chronic malnutrition which is very frequent in the cancer patients, thereby leading to higher risk of developing complications, lengthening the hospital stay, and inflating treatment cost.[33]

McMillan *et al*. demonstrated that body's inflammatory response to cancer cells (as measured by C-reactive protein) correlated with serum albumin levels.[32] Recently, increased levels of C-X-C motif ligand 10 (CXCL10), an inflammatory biomarker in DLBCL, has been shown to be significantly associated with high tumor burden and low serum albumin.[34] The Chinese and French researchers documented that plasma levels of interleukin-9 (IL-9) and IL-10 correlated with high IPI and low serum albumin in DLBCL cases.[35,36] Finally, serum albumin is also often used as a biochemical marker of nutrition status in oncology patients; with low serum albumin often associated with low BMI or lean body mass.[37] Our study also demonstrated a significant correlation of serum albumin with low BMI (<18.5 kg/m^2). The low serum albumin levels also tend to alter the pharmacokinetics of the chemotherapeutic agents such as steroids, vincristine, and doxorubicin used in the treatment of DLBCL. These drugs are highly protein bound and decreased albumin levels lead to increased risk of toxicity due to delayed elimination.[38] As a result, these patients have poor tolerance to chemotherapy and develop toxicity more frequently which lead to frequent treatment delays and dose modifications. Interestingly, of the 10 toxic deaths due to febrile neutropenia in the present study, 8 (80%) had serum albumin <3.5 g/dl.

The main limitation of our study was its retrospective nature and relatively small number of patients. We noticed that our data were skewed with majority of our patients (58.5%) presenting with advanced disease (Stage III and IV). This may be due to the fact that most DLBCL patients in our country are picked up late in their disease course due to delayed diagnosis and referral.

Conclusion

This study to the best of our knowledge is the first Indian study to demonstrate the independent prognostic significance of serum albumin in DLBCL patients in rituximab era. It also confirmed the validity of NCCN-IPI prognostic model in Indian patients. Serum albumin is a readily available, easy to standardize, and cheap investigation and holds promise for being incorporated in future DLBCL prognostic risk models. Whether serum albumin retains its prognostic significance in larger prospective treatment cohorts and in the era of targeted therapies/novel biomarkers needs to be investigated.

Acknowledgments

The study was carried out in Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow. We acknowledge the contribution of clinical hematologist Dr. R Kashyap for participation in the clinical management of patients. We also acknowledge the significant contribution of our Laboratory Hematopathologists – Dr. Ruchi Gupta and Dr. Khaliqur Rahman. We also acknowledge all clinical and laboratory hematology senior residents, and nursing staff without whom this study was impossible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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