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Pan-immune-inflammation value and body mass index to predict survival in diffuse large B-cell lymphoma

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Abstract

Background Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (NHL), constituting 31% of all NHL. Malignancy and inflammation are closely linked. Inflammatory processes have been identified to play an important role in the pathogenesis of lymphoma. Obesity is a well-known risk factor not only for the development of cardiovascular disease and diabetes but also for the development of several types of cancer, including lymphomas.

Objective To find out the association of pan-immune-inflammation value (PIV) and body mass index (BMI) with survival in adults with diffuse large B-cell lymphoma.

Patients and methods We conducted an observational retrospective study on 110 patients to unravel the association of PIV and BMI with survival outcome in a cohort of adults diagnosed as de novo DLBCL (NOS) and treated at the hematology units of International Medical Center, Helwan and Menoufia University Hospitals, in the period from 2014 to 2018.

Results The mean age of the studied patients was 54.27 years, the mean BMI was 28.91, and the median and IQR for PIV were 195.84 (96.20–498.52). The cutoff value for detecting mortality in BMI was 29.74 kg/m^2 with poor sensitivity (44.4%) and poor specificity (67.2%). The cutoff value for detecting mortality in PIV was 250.49 with poor sensitivity (50.0%) and poor specificity (67.2%). The mean duration of overall survival was 21.596 months. There was nonsignificant difference regarding 2-year overall survival according to BMI grouping (p-value = 0.195) and PIV grouping (p-value = 0.275).

Conclusion Neither PIV nor BMI were associated with 2-year overall survival in patients with DLBCL.

Keywords Diffuse large B-cell lymphoma, Pan-immune-inflammation value, Body mass index, Revised International Prognostic Index, Lugano staging, Survival

Introduction

NHL is the 10th most common cancer in the world in 2018 [1], while the most common NHL subtype is DLBCL, comprising approximately 30% of NHL [2]. In Egypt, lymphoma is considered the fourth most common tumor in adults; it represents 76.6% NHL and 23.4% HL [3]. DLBCL is the most common subtype of NHL in Egypt, representing about 49% of all NHL cases presenting to the National Cancer Institute (NCI) [4].

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Pro-inflammatory cytokines (or chemokines) and inflammatory cells and in tumor microenvironment were proved to promote tumor growth, DNA damage, angiogenesis, and immune suppression and to be associated with poor survival outcomes of patients [5–7]. Interleukin-10 (IL-10) is an immune regulatory cytokine [8]. Elevated plasma IL-10 levels correlated with adverse DLBCL features and poor prognosis and considered as a useful marker for evaluation of disease activity [9]. Programmed death ligand-1 (PD-L1) is responsible for T-cell activation, proliferation, and cytotoxic secretion to produce anti-tumor and immune responses [10]. High PD-L1 expression in DLBCL is associated with aggressive clinicopathological features and a decreased response to R-CHOP [11].

Recently, a new biomarker that takes into account all routinely assessed blood cell populations reflecting systemic inflammation and immunity, i.e., neutrophils, monocytes, lymphocytes, and platelets, has been proposed as a stronger and more reliable predictor of clinical outcomes in patients with advanced colorectal cancer [12].

Neutrophil to lymphocyte (NLR) is a reliable marker for polymorphonuclear leukocyte (PMNL) [13] and considered as an effective and noninvasive biomarker for poor prognosis and aggressive DLBCL [14]. Red cell distribution width (RDW) is a simple and immediately available inflammatory biomarker [15]. And its high level predicted an unfavorable prognosis in patients with DLBCL [16]. The mean platelet volume (MPV) describes the average platelet size reported in femtoliters, measures of the heterogeneity in platelet size [17]. Its low baseline is an independent prognostic marker of poor outcome in patients with DLBCL [18].

This biomarker, which was defined as pan-immune-inflammation value (PIV), is calculated by multiplying neutrophil count (10^3/mmc) by platelet count (10^3/mmc) and monocyte count (10^3/mmc) and finally dividing the result of this product by lymphocyte count (10^3/mmc) [19].

Obesity, a key modifiable factor and surrogate of many lifestyle factors, is increasing worldwide, and the prevalence is highest in the United States. High or low BMI is associated with increased all-cause mortality risk as well as cancer-specific mortality in some cancers such as breast cancer [20–22].

Patients and methods

On 110 patients, we conducted a retrospective study to elicit the association of PIV and BMI with survival outcome in a cohort of adults (≥ 18 years old) diagnosed as de novo DLBCL (NOS) according to the 2008 World Health Organization (WHO) classification of lymphoid neoplasm [23] and completed the standard R-CHOP protocol at the hematology units of International Medical Center, Helwan and Menoufia University Hospitals, from the beginning of 2014 until the end of 2018.

The patient's files were checked for the following:

A) Initial workup at diagnosis includes the following: Full history, comprehensive clinical examination with special emphasis on Eastern Cooperative Oncology Group (ECOG) [24], height (m^2), weight (kg), and BMI calculation (kg/m^2) and laboratory investigations: CBC, peripheral blood film, PIV calculation [25], kidney, liver function tests, HCVAb, HBsAg, HBcAb and HIVAb, ESR, CRP, LDH, B2 microglobulin, Revised International Prognostic Index (R-IPI) risk stratification [26], and Lugano staging.
B) Response evaluation (according to Lugano classification criteria) [27, 28].

Statistical analysis

The data collected were tabulated and analyzed by SPSS (Statistical Package for Social Sciences) version 23.0 on IBM compatible computer (SPSS Inc. Released 2015. IBM SPSS statistics for Windows version 23, Armonk, NY, USA: IBM Corp.). Two types of statistics were done: Descriptive statistics, e.g., percentage (%), mean (x), and standard deviation (SD), and analytic statistics, e.g., univariate and multivariate regression analysis which measure the relationship between the categorical dependent variables and one or more independent variables. Overall survival (OS) was done to define the prognostic indices such a case. Receiver operator characteristic (ROC) curve was done to determine the cutoff value, sensitivity, and specificity of the studied variables.

Results

Our study showed that 63.6% of the studied patients were males; most of them (69.1%) were stages III and IV by Lugano staging. Extranodal disease was present in 46.4% of the studied group, associated comorbidity and bone marrow involvement were present in 59.2% and 45.5% of the studied patients respectively, R-IPI was good among most of the studied group (58.2%), and LDH was above ULN in 37.3% only as shown in Table 1. The mean duration of overall survival was 21.596 months. A total of 58.2% of the studied patients were alive until the end of this duration, while 25.4% were lost, and 16.4% were died (Table 2). The cutoff point for detecting mortality in BMI was 29.74 kg/m^2 with poor sensitivity (44.4%) and poor specificity (67.2%) (Table 3), while the cutoff point for detecting

Table 1 Baseline characteristics of the studied DLBCL patients ($n = 110$)

Parameter	Value
Age in years (mean ± SD)	**54.27 ± 12.94**
Male sex (no. & %)	**70 (63.6%)**
Lugano staging (no. & %)	
Stages I & II	**34 (30.9%)**
Stages III & IV	**76 (69.1%)**
Extranodal disease	
Yes (no. & %)	**51 (46.4%)**
ECOG (no. & %)	
< 2	**110 (100%)**
LDH (no. & %)	
> ULN	**41 (37.3%)**
R-IPI (no. & %)	
Very good	**26 (23.6%)**
Good	**64 (58.2%)**
Poor	**20 (18.2%)**
Bone marrow involvement (no. & %)	**50 (45.5%)**
BMI in kg/m^2 (mean ± SD)	**28.91 ± 4.93**
PIV	
Median (IQR)	**195.84 (96.20–498.52)**
Comorbidity (no. & %)	**64 (59.2%)**

ECOG Eastern Cooperative Oncology Group, *LDH* Lactate dehydrogenase, *ULN* Upper limit normal, *SD* Standard deviation, *R-IPI* Revised International Prognostic Index, *BMI* Body mass index, *PIV* pan-immune-inflammation value, *IQR* Interquartile range

Table 2 Two-year survival outcome among the studied patients

Outcome	No	%
Alive	64	**58.2%**
Censored	28	**25.4%**
Ceased	18	**16.4%**

mortality in PIV was 250.49 with poor sensitivity (50.0%) and poor specificity (67.2%) (Table 4). There was insignificant difference regarding 2-year overall survival according to BMI grouping (p-value = 0.195) and PIV grouping (p-value = 0.275) (Tables 5, 6). The age, sex, and poor R-IPI were significant predictors for mortality on univariate analysis; p-values were 0.004 < 0.001 and 0.004, respectively, but these predictors lost their significance on multivariate analysis; and p-values were 0.985, 0.076, and 0.149, respectively, while Lugano staging, LDH, bone marrow involvement, PIV, and BMI were insignificant predictors for mortality on univariate analysis (Table 7) (Figs. 1, 2, 3, 4, 5, 6).

Discussion

DLBCL is the most common type NHL accounting for 30–40% of B-cell NHL (B-NHL). The incidence rises with age, reaching a median age at diagnosis in the seventh decade. However, DLBCL can occur at any age, with a slight predominance in males [29–31].

In the last two decades, the relationship between chronic inflammation and cancer has become very popular, and both the diagnostic and therapeutic value of inflammatory markers have been studied extensively. Inflammation has been shown to promote tumor initiation and progression, whereas escape from immune surveillance may favor cancer invasiveness [32]. In the tumor microenvironment, neutrophils, monocytes-derived macrophages, and platelets have adverse prognostic significance by promoting tumoral angiogenesis and tumor growth, whereas tumor-infiltrating lymphocytes portend favorable outcomes [33, 34].

Obesity and cancer have been linked in a cause and effect relationship as supported by several reports. Obesity-related cancers are becoming more common, making this disease spectrum a public health priority [35].

Medical oncologists are frequently confronted with overweight and obese patients, including their specific set of comorbidities [36] and differential pharmacokinetics [37]. Drug distribution and elimination are reported to be influenced by obesity, an effect especially relevant for lipophilic drugs [38]. Drug metabolism may be altered by obesity-induced liver steatosis and changed hepatic blood flow, as well as the partially increased enzymatic activity of the cytochrome P450

Table 3 ROC curve for BMI in kg/m^2

Cutoff point	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	*p*-value
29.74	44.4%	67.2%	57.51	54.72	0.530	0.365–0.694	**0.703**

ROC Receiver operator curve, *PPV* Positive predictive value, *NPV* Negative predictive value, *AUC* Area under curve, *CI* Confidence interval

Table 4 ROC curve for PIV

Cutoff point	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	*p*-value
250.49	50.0%	67.2%	60.38	57.34	0.540	0.365–0.715	**0.606**

Table 5 Two-year overall survival according to BMI

Parameter	≤ 29 kg/m^2 (*N* = 56)	> 29 kg/m^2 (*N* = 54)	Log rank	*p*-value
Alive	29 (51.8%)	35 (64.8%)	0.011	**0.915**
Censored	18 (32.1%)	10 (18.5%)		
Ceased	9 (16.1%)	9 (16.7%)		
Mean OS in months	21.393	21.776		
CI 95%	19.811–22.975	20.305–23.247		

Table 6 Two-year overall survival according to PIV

Parameter	Low ≤ 250.49 (*N* = 56)	High > 250.49 (*N* = 54)	Log rank	*p*-value
Alive	37 (66.1%)	27 (50.0%)	1.193	**0.275**
Censored	12 (21.4%)	16 (29.6%)		
Ceased	7 (12.5%)	11 (20.4%)		
Mean OS in months	22.116	21.084		
CI 95%	20.706–23.526	19.485–22.683		

Table 7 Uni- and multivariate Cox regression analyses for predictors of overall survival

Parameter	Univariate analysis			Multivariate analysis		
	HR	CI 95%	*p*-value	HR	CI 95%	*p*-value
Age group						
> 60 years	0.241	0.091–0.644	0.004	1.015	0.211–4.878	**0.985**
Male sex	0.133	0.044–0.404	< 0.001	3.364	0.883–12.819	**0.076**
Lugano stage						
III & IV	0.431	0.125–1.489	0.183	------	------	-----
Presence of extranodal	0.392	0.140–1.101	0.075	------	------	------
LDH >=ULN	0.406	0.160–1.032	0.058	----	------	--------
RIPI						
Very good	--------	--------	--------	-------	--------	-------
Poor	0.004	2.666–198.022	0.004	0.177	0.017–1.860	**0.149**
Good	0.456	0.245–22.922	0.456			
Bone marrow involvement	0.16	0.198–1.308	0.16	-----	------	------
PIV	0.946	0.999–.001	0.946	------	-----	-----
BMI	0.317	0.960–1.134	0.317	------	------	-----

HR Hazard ratio

superfamily in obese individuals [39]. Underdosing of chemotherapy is frequently seen in patients with a calculated body surface area of > 2 m^2 [40], and a higher body mass index (BMI) might, in part, counterbalance tumor cachexia in advanced disease.

Our study was conducted on 110 patients. As regard the baseline characteristics of the studied patients, the mean age was 54.27 years. Our study showed male predominance as 63.6% of the studied patients were males; most of them (69.1%) were stages III and IV by Lugano staging. Extranodal disease was present in 46.4% of the studied group, associated comorbidity and bone marrow involvement were present in 59.2% and 45.5% of the studied patients respectively, R-IPI was good among most of the studied group (58.2%), and LDH was above ULN in 37.3%.

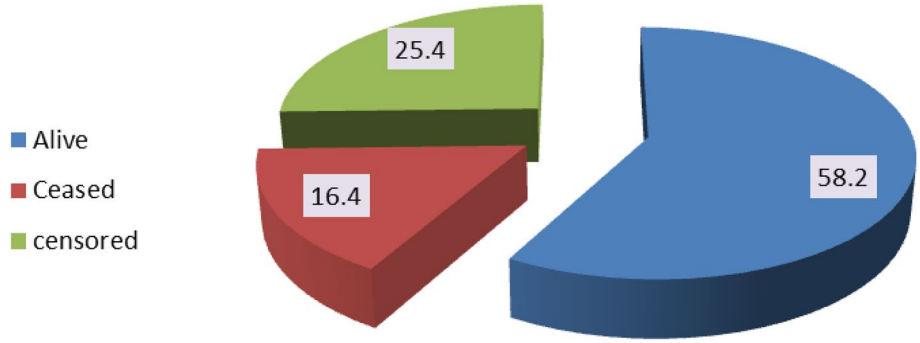

Fig. 1 Two-year survival outcome among the studied patients

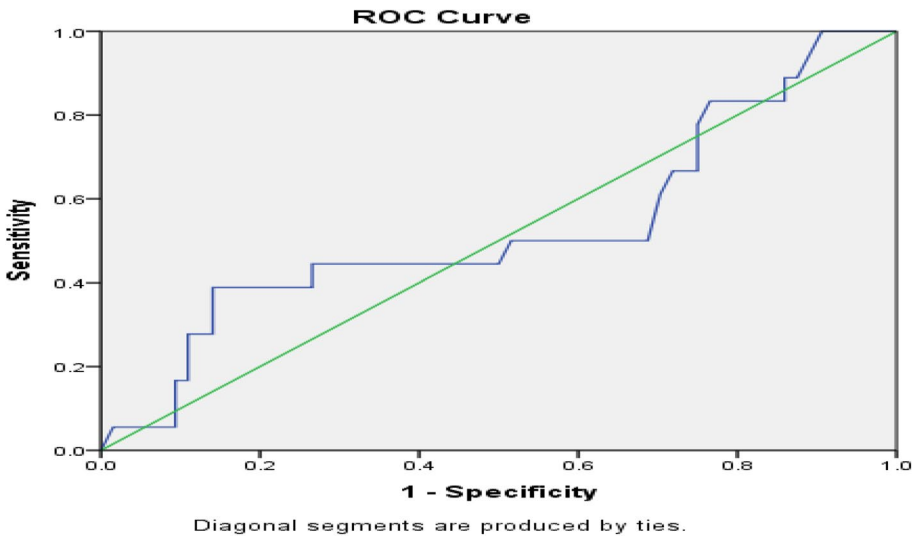

Fig. 2 ROC curve for BMI

Regarding our study, the cutoff point for detecting mortality in PIV was 250.49 with poor sensitivity (50.0%) and poor specificity (67.2%). There was insignificant difference regarding 2-year overall survival according to PIV grouping (p value = 0.275).

According to our knowledge, our study is the first to unravel the association of PIV with survival in adults with DLBCL.

While Ligorio et al. found that high PIV was associated with worse OS in Human Epidermal Growth Factor Receptors Positive Advanced Breast Cancer (HER2+aBC) patients treated with first line trastuzumab-pertuzumab-containing biochemotherapy [26].

Against our results, Fuca et al. found that PIV showed a strong association with progression-free survival (PFS) and OS in patients with advanced colorectal cancer, and the prognostic value of the PIV was stronger than that of other well-established immune-inflammatory biomarkers (e.g., NLR). OS & PFS were significantly longer in patients with low baseline PIV as compared to high PIV [19].

According to our study, the cutoff point for detecting mortality in BMI was 29.74 kg/m^2 with poor sensitivity (44.4%) and poor specificity (67.2%). There was insignificant difference regarding 2-year overall survival according to BMI grouping (p-value = 0.195).

Unlike Chihara et al. who found that obesity before the time of diagnosis but not at the time of diagnosis was associated with shorter lymphoma specific survival (LSS) in patients with follicular lymphoma (FL). But similar to our study, BMI was not associated with survival following DLBCL and chronic/small lymphocytic leukemia (CLL/SLL), except for individuals who were under weight or who experienced decrease in BMI

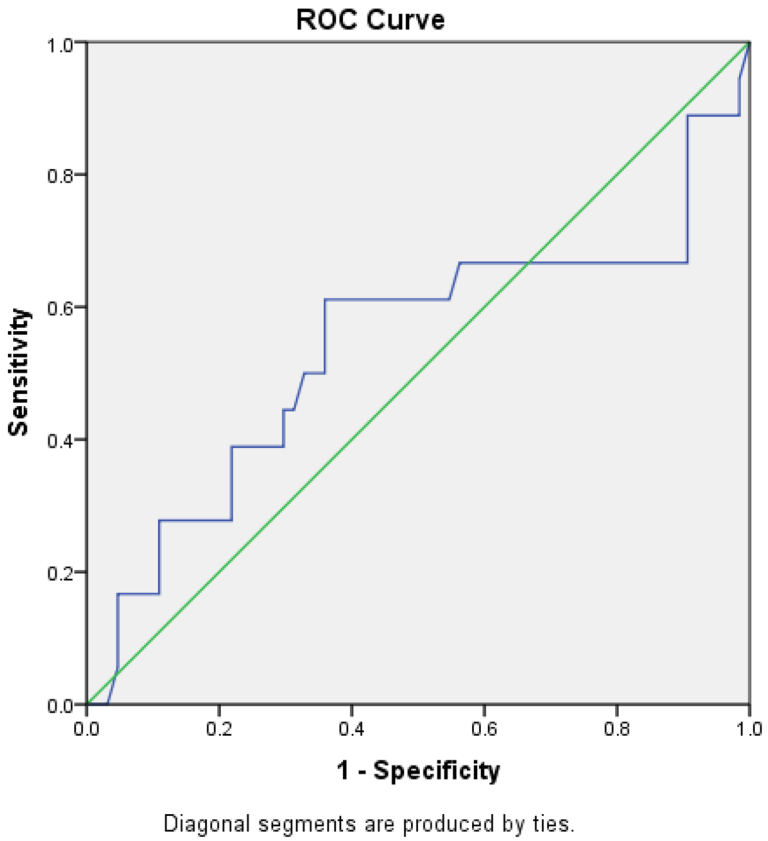

Fig. 3 ROC curve for PIV

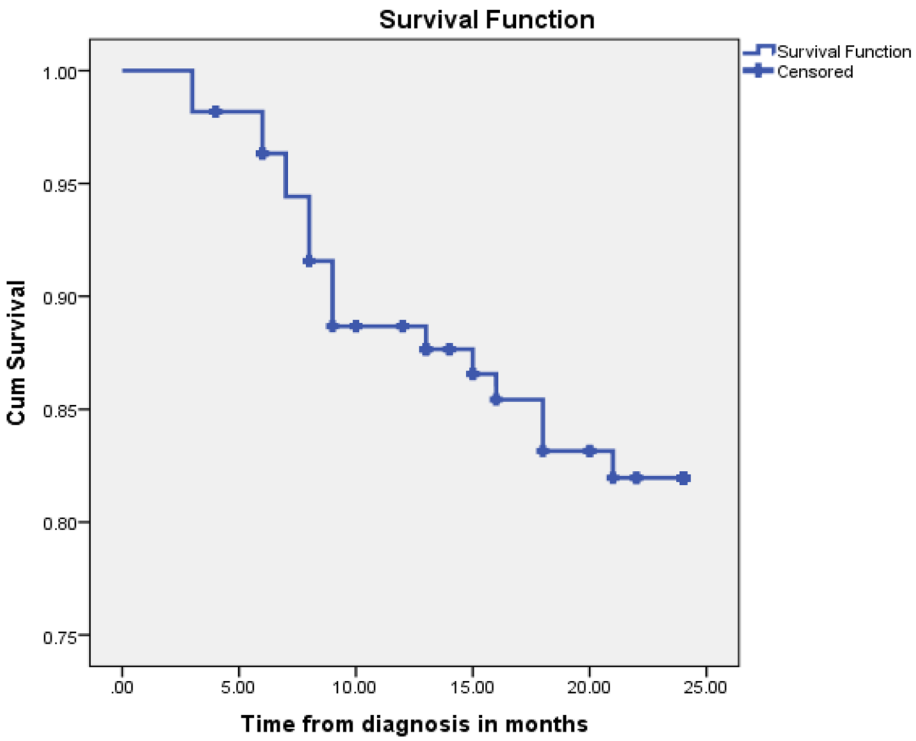

Fig. 4 Two-year overall survival of the studied patients

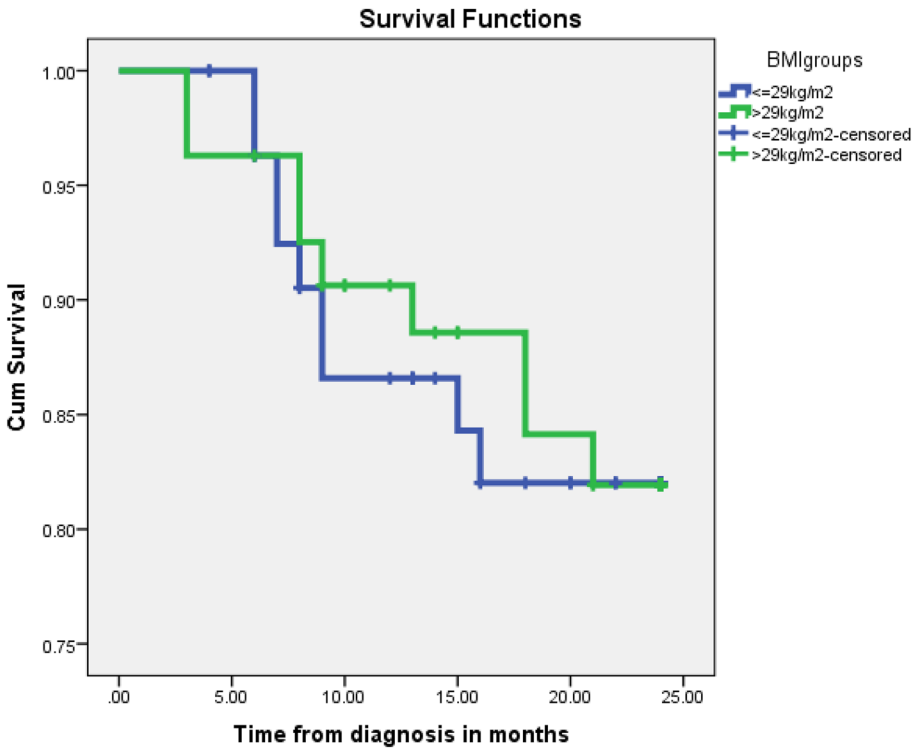

Fig. 5 Two-year overall survival of the studied patients according to BMI

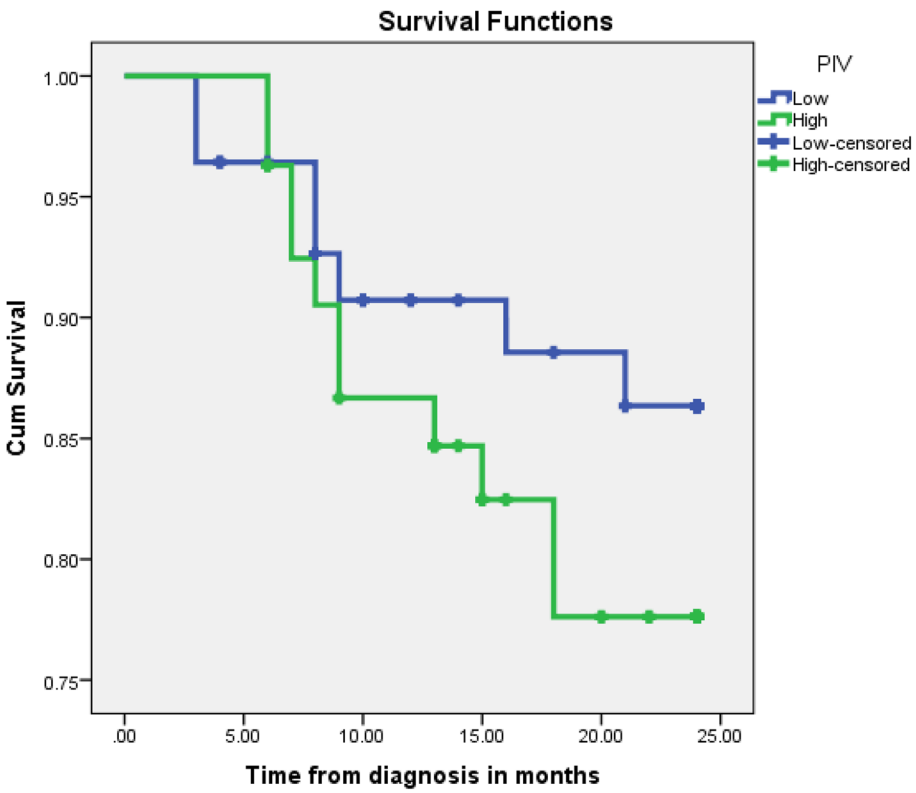

Fig. 6 Two-year overall survival of the studied patients according to PIV

prior to diagnosis, which likely represents lymphoma-related weight loss [28].

The lack of association that they observed between BMI prior or BMI at the time of diagnosis (BMI-dx) for survival outcomes in DLBCL and CLL/SLL was consistent with the US intergroup study that evaluated patients who were treated on three Eastern Cooperative Oncology Group (ECOG) phase III clinical trials and the Scandinavian Lymphoma Etiology study [41, 42].

While *Gay et al.* showed that patients who have high body surface area (BSA), which significantly correlates with high BMI, tend to have higher treatment-related mortality, but the dose capping of anthracycline by BSA was not associated with survival outcomes in DLBCL [43].

Recently, a cancer registry analysis reported significantly prolonged OS for overweight (BMI 25 to < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) patients with diffuse large B-cell lymphoma (DLBCL) when compared with normal weight patients that was against our study [44, 45].

Conclusion

Neither PIV nor BMI were associated with 2-year overall survival in patients with DLBCL.

Recommendation

Finally, we acknowledge the limitation of our study due to its retrospective design, short duration and limited number of patients recommending a prospective study design, long duration, and large number of patients.

Abbreviations

AUC	Area under curve
BMT	Bone marrow transplantation
BMI	Body mass index
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CRP	C-reactive protein
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte sedimentation rate
FL	Follicular lymphoma
HBcAb	Hepatitis B virus core antigen
HBsAg	Hepatitis B virus surface antigen
HCVAb	Hepatitis C virus antibody
HIVAb	Human immunodeficiency virus antibody
HR	Hazard ratio
IQR	Interquartile range
LDH	Lactate dehydrogenase
LSS	Lymphoma-specific survival
NLR	Neutrophil-lymphocyte ratio
NOS	Not otherwise specified
NPV	Negative predictive value
OS	Overall survival
PFS	Progression-free survival
PIV	Pan-immune-inflammation value
PPV	Positive predictive value
R-IPI	Revised International Prognostic Index
ROC	Receiver operator characteristic
ROC	Receiver operator curve
SD	Standard deviation
SLL	Small lymphocytic leukemia
SPSS	Statistical Package for Social Sciences
ULN	Upper limit normal

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Authors' contributions

Mohamed Ahmed Abdelhafez wrote the manuscript & analyzed the data.
Sara Gamal Elmeligy & Rania Mohamed Afifi performed data collection & manuscript preparation.
Sabry Abdullah Shoeib & Mahmoud Salah Abdelsalam were responsible for the selection & follow up of patients.
All authors revised the study & reviewed the article.
All authors ensured,investigated & resolved any questions related to accuracy or integrity of any part of the work.

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Availability of data and materials

Data are available upon request.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare no competing interests.

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