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ORIGINAL ARTICLE

Impact of Prognostic Nutritional Index and Systemic Immune-Inflammation Index on the Clinical Outcome of Diffuse Large B Cell Lymphoma Patients Treated with RCHOP

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ABSTRACT

Background: The most frequent lymphoma in Egyptian adults is diffuse large B-cell lymphoma (DLBCL). Patients with DLBCL experienced a wide variety of prognoses. It has become challenging to identify high-risk groups using IPI alone because the outcome of DLBCL patients has improved with the introduction of rituximab. It would thus be important to find prognostic indicators for predicting patient subgroups with poor prognosis and choose the efficient therapy regimen in accordance. One of the factors thought to contribute to the formation of cancer metastases and cancer progression is inflammation. The systemic immune inflammation index (SII) is a reliable indicator of cancer patients' prognosis. It seems that nutritional status affects how different solid tumors behave. To evaluate the immunological nutritional condition of cancer patients, the Prognostic Nutritional Index (PNI) was developed. The goal of our research was to assess SII and PNI's prognostic and predictive significance in DLBCL patients receiving RCHOP therapy.

Method: This prospective, non-randomized study aimed to evaluate the prognostic value of SII and PNI in patients DLBCL receiving RCHOP. Eighty-four patients were included.

Results: The optimal cut-off values for PNI and SII using the ROC curve were 50 and 410, respectively. PNI and SII were significantly associated with a complete remission rate. Multivariate analyses showed that low PNI and high SII were independent predictors of poor relapse-free and overall survival.

Conclusions: A growing body of evidence demonstrates the value of pretreatment PNI and SII as simple prognostic indicators in DLBCL patients receiving RCHOP.

Keywords: Systemic inflammation index, prognostic nutritional index, DLBCL, Rituximab

INTRODUCTION

The most frequent lymphoid neoplasm in adults is diffuse large B-cell lymphoma (DLBCL), which accounts for around 32.5% of non-Hodgkin lymphomas (NHL) identified each year [1]. In Egypt, DLBCL is the most prevalent NHL (55%) [2].

Patients with DLBCL experience a wide variety of symptoms and prognoses. The International Prognostic score (IPI) was formerly considered the most trustworthy prognostic score for NHL patients undergoing CHOP treatment [3].

It has become challenging to identify high-risk groups using IPI alone because the outcome of DLBCL patients has improved so much with the introduction of rituximab [4]. Although the overall survival (OS) of patients with DLBCL has improved in the rituximab era, one-third of the patients are still resistant to the first-line treatment or relapse after initial remission [5].

Thus, it would be important to find prognostic indicators for predicting patient subgroups with

poor prognoses and choose an efficient therapy regimen.

The revised IPI (R-IPI) and NCCN-IPI were created to risk-stratify patients who received R-CHOP. Compared to IPI, the R-IPI redistributes the IPI clinical scores into three groups, improving clinical outcome prediction [6]. In order to categorize patients into four categories, the NCCN-IPI is also calculated based on various clinical parameters, including a more accurate description of extranodal site involvement and an improved evaluation of age and Lactate dehydrogenase (LDH) [7]. Also additional predictive factors have been found to include gene expression profiling [9] and molecular genetic markers [8].

However, these indicators are cumbersome, expensive, difficult to use in routine clinical practice, and unable to forecast prognosis accurately. Therefore, there is a pressing need to create affordable, straightforward, and accessible prognostic biomarkers.

The growth of tumors and inflammation are tightly related [10]. Additionally, it is crucial to the tumor's development and the treatment's effectiveness. Immune cells constantly release cytokines and chemokines to control the tumor microenvironment and shape tumor progression. The Interleukin 4 (IL-4) and interleukin 10 (IL-10) produced by neutrophils in the tumor microenvironment can encourage tumor development, invasion, and angiogenesis [11]. Therefore, increased neutrophil numbers may impact a DLBCL's ability to survive. In solid tumors, it has been discovered that platelets can prevent Natural killer (NK) cell-mediated death of circulating cancer cells, enhance cancer cell metastasis, and produce cytokines to promote tumor cell proliferation [12].

The cytotoxic action of rituximab on tumor cells is mostly caused by lymphocytes [13]. Low lymphocyte counts have been linked to poor outcomes in DLBCL patients, according to earlier research [14]. Additionally, Dehghani et al. showed that an increased number of Treg cells was related to a better prognosis in DLBCL patients undergoing R-CHOP [15]. Therefore, the progression of malignancies is tightly correlated with peripheral blood counts, which partially reflect the condition of inflammation [16]. Pretreatment neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are two examples of inflammatory markers that have been shown to significantly affect the outcomes of DLBCL patients in recent research [17, 18]. Moreover, these blood biomarkers are more accessible and less expensive than molecular genetic markers.

The outcome of numerous solid malignancies, pancreatic cancer [19], breast cancer [20], lung cancer [21], and gastrointestinal cancer [22], has been linked to a high systemic immune-inflammation index (SII), which is calculated based on neutrophil, platelet, and lymphocyte counts.

The clinical outcomes of patients with different solid tumors and surgical sequelae strongly correlate with nutritional conditions. Recently, it has been shown that various indications with nutritional and inflammatory variables might help predict how well cancer patients, including those with colorectal and esophageal cancer, would do [23]. Additionally confirmed as a helpful prognostic indicator in many malignancies, including esophageal carcinoma and osteosarcoma, is the Prognostic Nutritional Index (PNI) [24].

Malnutrition, a problem that patients with DLBCL frequently experience has been linked to poor overall survival in several studies conducted recently [25]. Patients with lymphoma who receive inadequate nourishment are more likely to experience febrile neutropenia, which can delay chemotherapy treatment since fewer drugs are being used.

No matter the location or origin of the tumor, recent studies have shown that PNI can be utilized to predict the clinical outcomes of patients with various malignant tumors [26], [27]. Various studies have examined the predictive usefulness of PNI for DLBCL, although the findings were mixed and conflicting [28, 29].

The link between PNI, SII, and clinical outcomes in patients with DLBCL treated with RCHOP has not been established despite mounting evidence that SII and PNI can reliably predict cancer patient prognosis. This study's primary goal is to assess the predictive significance of SII and PNI in DLBCL treated with RCHOP.

In this study, we sought to evaluate the prognostic and predictive significance of SII and PNI in DLBCL patients receiving RCHOP.

METHODS

Compliance with Ethical Standards

This study was approved by the Zagazig University Institutional Review Board (IRB) and carried out from May 2021 to March 2023 at Zagazig University and El-Mabara Hospitals.

Study design and settings:

This prospective, non-randomized study included 84 patients with CD20-positive DLBCL who presented to the Medical Oncology Department, Zagazig University Hospital, and El-Mabara

Hospitals during the study period. Patients had to be at least 18 years old, had never received radiation or chemotherapy, and had no medical conditions that would preclude them from getting R-CHOP. Patients who were HIV positive, breastfeeding, or pregnant were not allowed to participate. Patients with primary central nervous system (CNS) lymphoma or composite lymphoma were also excluded.

Pretreatment Evaluation:

Pretreatment evaluation included history; physical examination; laboratory studies (blood counts, LDH, liver and kidney functions), and virology serology (HCV Ab, HBsAg, HBcAb, PCR for serologically positive patients); and bone marrow biopsy when there was unexplained cytopenia. Staging radiology included PET-CT scans whenever possible and/or CT scans of the chest, abdomen, and pelvis. According to the Lugano adaptation of the Ann Arbor staging system, patients were staged. We employed standard IPI, NCCN-IPI, to divide our patients into several prognostic groups, and performance status was reported using the Eastern Cooperative Oncology Group performance scale.

Pretreatment PNI and SII:

The PNI was calculated as the level of albumin (g/L) summed to the total number of lymphocytes (10^9 /L) multiplied by 5 [24]. The SII was defined as the number of platelets multiplied by neutrophils and divided by the number of lymphocytes (10^9 /L) [19]. PNI and SII cut-off levels were established using Receiver Operating Characteristic (ROC) curves based on patient overall survival (OS).

Treatment Schedule:

R-CHOP therapy (rituximab 375 mg/m2 day 1, cyclophosphamide 750 mg/m2 day 1, doxorubicin 50 mg/m2 day 1, vincristine 1.4 mg/m2 day 1, prednisone 100 mg PO daily for five days) was prescribed to patients who met the eligibility requirements. Six cycles of R-CHOP-21 were planned for eligible patients with no contraindications to treatment. Patients with bulky disease (7.5 cm) were given locoregional RT (36 Gy). According to the Common Terminology Criteria for Adverse Events (CTCAE v4.0), adverse events were documented and categorized.

Laboratory Methods

The blood samples were collected and placed in BD Vacutainers **(Becton, Dickinson and Company, Franklin Lakes, NJ).** Each patient was given one citrate, plain, and EDTA tube. Immediately, a 2000 x g centrifuge was used to spin the citrate tube for 15 minutes. Thirty minutes after the collection in the plain tube, the serum was separated by centrifuging the tube at 1200 x g for ten minutes.

Sysmex, Kobe, Japan's XS500i Hematology analyzer, performed the full blood picture from the EDTA tube. The blood film was utilized to determine the differential cell count. The prothrombin time (PT) was determined using the Sysmex CS2100i **(Siemens, Munich, Germany).** All biochemical tests were examined using the Cobas 8000 Modular Analyzer **(Roche Diagnostics, Mannheim, Germany).**

Response Assessment:

Response Evaluation Criteria In Solid Tumors (RECIST) was used to evaluate the tumor response based on radiological evaluations such as CT, MRI, and PET scans [30]. After 3-4 cycles of RCHOP and before RT, if planned, interim restaging (using CT scans) was performed. Upon completion of treatment, an end-of-treatment restaging using PET-CT scans was performed. If interim staging showed a CR or partial response (PR), the planned course of treatment was completed. After completion of treatment, clinical follow-up at regular intervals (every 3-6 months for five years and annually after that or as clinically indicated) was recommended for patients with CR. Patients with PR and those who did not respond to treatment or whose disease progressed at any time during treatment were treated with salvage treatment as described for relapsed or refractory disease, followed by HDT/ASCR if CR was achieved.

STATISTICAL ANALYSIS

The data distribution was not parametric (Shapiro-Wilk test). Thus, categorical data were shown as frequencies and percentages, while quantitative factors were shown as the median and range. Categorical variables were compared using the chi-squared test. The PNI and SII cut-off values based on patient survival were found using receiver operating characteristics (ROC) curve analysis. Spearman correlation analysis was utilized to find an association of variables. Relapse-free survival (RFS) was determined as the interval between the beginning of chemoimmunotherapy and the time relapse was confirmed or the most recent follow-up at which the patient was relapse-free. The time from diagnosis to death or the most recent follow-up contact (censored) was used to calculate overall survival (OS). Kaplan-Meier survival curves were created to assess the survival patterns, and the significance was found using the log-rank test. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated using the univariate and multivariate Cox proportional hazards model. A p-value of 0.05 or less was considered significant. Statistical analysis was done using

SPSS 17 software **(SPSS Inc., IL, USA).**

RESULTS

Baseline Characteristics:

Table 1 provides an overview of the demographic, clinicopathologic, and laboratory characteristics of 84 non-Hodgkin lymphoma patients included in our study. The mean age of patients was 52.23 years. Fifty-nine patients (70.2%) had age less than 60 years. Forty-five patients (53.6%) were males. Twenty-six patients (31%) had comorbidities; diabetes and hypertension were detected in 19% and 14.3% of patients, respectively. Eighteen patients (21.4%) had extranodal sites. Muscles were the most common extranodal site (7 patients, 8.3%), followed by stomach (4 patients, 4.8%). Thirty-seven patients (44%) had stage III disease. The mean white blood cell count was $7.87x10^3$/cc. The mean neutrophil count was $4.46x10^3$/cc. Mean lymphocyte count was 2.19 $x10^3$/cc. The mean platelet count was 229.05 $x10^3$/cc. The mean albumin level was 3.94g/dl. Thirty-four patients (40.5%) had low to intermediate international prognostic index (IPI). Forty-seven patients (56%) had low to intermediate NCCN international prognostic index (IPI). Eighteen patients (21.4%) had bulky sites. Thirty-three patients (39.3%) had B symptoms. Twenty-two patients (26.2%) had positive HCV antibodies. Four patients (4.8%) had positive HCV PCR. Six patients (7.1%) had positive hepatitis B surface antigen. Three patients (3.6%) had positive hepatitis B core antibody. All three patients had an undetectable HBV viral load by PCR. Tenofovir 300 mg per day was prescribed prophylactically to patients who tested positive for HBcAb. The patient's viral load was monitored monthly during treatment and every three months afterward. Fortunately, her viral load was undetectable, so full RCHOP treatment was performed as planned. Antiviral treatment was continued as recommended by the hepatologist until the end of his follow-up period.

PNI and SII Cut-off Values:

The mortality prediction properties of PNI and SII were assessed using ROC curve analysis (Figure 1A, 1B). PNI demonstrated 80% sensitivity and 71.9% specificity with a PNI value 50. With a 410 SII cut-off, 95% sensitivity and 64.1% specificity were reported. Thirty-four patients (40.5%) were assigned to the PNI-low group based on the PNI cut-off (50), while the remaining 50 patients (59.5%) were assigned to the PNI-high group. Thirty-one patients (36.9%) were classified as being in the SII-high group, while the remaining 53 patients (63.1%) were in the SII-low group, based on the SII cut-off (410).

Treatment and toxicity:

Three patients (3.6%) discontinued treatment, one due to toxicity and two because of progressive disease. Nineteen patients (22.6%) had grade 1 hyperbilirubinemia. Twelve patients (14.3%) had grade 1 hypoalbuminemia. Twenty-one patients (25%) had grade 1 elevation of AST. Eighteen patients (21.4%) had grade 1 elevation of ALT. Four patients (4.8%) had grade 1 ascites. Ten patients (11.9%) had grade 1 prolongation of INR. Eleven patients (13.1%) had grade 1 elevation of serum creatinine. Sixteen patients (19%) had grade 1 neutropenia. Sixteen patients (19%) had grade 1 anemia. Eleven patients (13.1%) had grade 1 thrombocytopenia. Four patients (4.8%) had grade 3 peripheral neuropathy. Two patients (2.4%) had grade 1 infusion/allergic reactions (table 2).

Response and Survival:

Twenty-four patients (28.6%) had either refractory disease or progressive disease. The median follow-up duration was thirteen months. Of 60 patients who had complete remission, eleven patients (18.3%) had relapsed disease. By the end of the follow-up duration, sixty-four patients (76.2%) were alive, and twenty patients (23.8%) died. Seven patients (8.3%) were alive with refractory or progressive disease. Five patients (6%) had died due to liver cell failure secondary to hepatitis C viral activation related to salvage chemotherapy. Five patients (6%) had died due to sepsis related to salvage chemotherapy (Table 2). The median follow-up period was 13 months. The median overall survival (OS) was 18.3 months. Relapse-free survival (RFS) was 11.6 months.

PNI, SII and Response Rates:

According to a Spearman correlation study (r= -0.28, p=0.011), PNI and SII had a negative association. PNI and SII were related to the response rate. Significant associations between PNI, SII, and the relapse rate were identified (Table 3).

The Prognostic Value of PNI and SII in NHL Patients:

We examined the prognostic value of PNI and SII in DLBCL patients. Table 4 displays how the OS and RFS vary regarding the PNI and SII values. In Figure 1 C-F, the Kaplan-Meier curves were displayed. Between the PNI-low group and PNI-high group, as well as between the SII-low group and SII-high group, log-rank tests revealed statistically significant differences.

Univariate & multivariate Analyses for Prognostic Variables:

In the univariate OS study, high PNI was linked to a low HR of 0.08 (95% CI: 0.03-0.25; p0.001). Furthermore, a high HR of 32.2 (95% CI: 4.2-243;

p=0.001) was associated with a higher SII. High PNI was connected to a low HR of 0.14 (95% CI: 0.04-0.48; p=0.002) in terms of RFS; however, high SII was connected to a high HR of 14.8 (95% CI: 3.1-72.7; p=0.001). Table 5 also included other variables associated with survival.

PNI and SII were still significantly linked with survival in the multivariate analysis that considers all factors listed in Table 5's data. Regarding OS, HR was 0.16 (95% CI: 0.04-0.65; p=0.01) for high PNI. HR was 18.4 (95% CI: 1.9-180.8; p=0.013) for high SII. The RFS multivariate analysis revealed that high PNI had an HR of 0.01 (95% CI: 0-0.23; p=0.01) for it. High SII was associated with RFS and had an HR of 67.7 (95% CI: 5.6-81.1; p=0.015).

Table 1: Baseline characteristics of the lymphoma patients.

Parameters	lymphoma patients (No.: 84)
Age, years	50 [25-72y]
Sex, Male/Female	45/39 (53.6/46.4%)
Comorbidities	26 (31%)
Diabetes	16 (19%)
Hypertension	12 (14.3%)
Viral markers	
HCV Antibody	22 (26.2%)
HBV surface Antigen	6 (7.1%)
ECOG Performance Status Scale	
ECOG 0	51 (60.7%)
ECOG 1	27 (32.1%)
ECOG 2	5 (6%)
ECOG 3	1 (1.2%)
LDH	
Elevated	55 (65.5%)
Extranodal site	18 (21.4%)
One site	14 (16.7%)
Two or more	4 (4.8%)
Bulky sites	18 (21.4%)
B symptoms	33 (39.3%)
Staging	
II	19 (22.6%)
III	37 (44.1%)
IV	28 (33.3%)
IPI	
Low	31 (36.9%)
Low – Intermediate	34 (40.5%)
High – Intermediate	19 (22.6%)
NCCCN-IPI	
Low	11(13%)
Low – Intermediate	47 (56%)
High – Intermediate	26 (31%)
Laboratory tests	Mean [Range]
WBCs, $*10^9$/L	7 [3.2-18]
Neutrophils, $*10^9$/L	4 [1.4-12.5]
Lymphocytes, $*10^9$/L	2.1 [0.9-5.6]
Platelets, $*10^9$/L	215 [79-547]
Albumin, g/dL	4.1 [1.83-5.22]
Prognostic variables	
PNI cut-off [range]	52.2 [33.8-65]
Low-group (≤ 50)	34 (40.5%)
High-group (> 50)	50 (59.5%)

Parameters	lymphoma patients (No.: 84)
SII cut-off [range]	410.3 [130.2-1246.9]
Low-group (≤ 410)	53 (63.1%)
High-group (> 410)	31 (36.9%)

No.: Number; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; IPI: International Prognostic Index; NCCCN: National Comprehensive Cancer Network; WBCs: White blood cells; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index. B symptoms refer to fever, drenching night sweats, and loss of more than 10 percent of body weight over six months. Data are expressed as number (%) or median [Min-Max]

Table 2: Treatment-related parameters in lymphoma patients

Parameters	Lymphoma patients (No.: 84)	
Withdrawal of treatment	3 (3.6%)	
Progressive disease	2 (2.4%)	
Toxicity	1 (1.2%)	
Adverse events	**All grades**	**Grade III-IV**
Hyperbilirubinemia	24 (28.6)	0
Hypoalbuminemia	17 (20.2)	1 (1.2)
Elevated AST	28 (33.3)	2 (2.4)
Elevated ALT	24 (28.6)	2 (2.4)
Ascites	7 (8.3)	0
INR prolongation	12 (14.3)	0
Elevated creatinine	14 (16.7)	1 (1.2)
Neutropenia	36 (42.9)	8 (9.5)
Anemia	24 (28.6)	0
Thrombocytopenia	18 (21.4)	4 (4.8)
Peripheral neuropathy	8 (9.5)	4 (4.8)
Allergic reaction	2 (2.4)	0
Follow-up duration, months	13 [2-42]	
Response		
Complete response	60 (71.7)	
Refractory/progression of disease	24 (28.6)	
Relapse	11 (18.3)	
Mortality	20 (23.8)	
Liver cell failure	5 (6)	
ARDS/Respiratory Failure	1 (1.2)	
Sepsis	6 (7.1)	
Renal Failure	1 (1.2)	
COVID/Respiratory Failure	5 (6)	
Stroke	1 (1.2)	
Hematemesis	1 (1.2)	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: international normalized ratio; ARDS: Acute respiratory distress syndrome; COVID: Coronavirus Disease.
Data are expressed as number (%) or median [Min-Max]

Table 3: Association between PNI, SII, and follow-up parameters

Parameters	PNI			SII		
	≤ 50	> 50	p	≤ 410	> 410	p
Response (84 patients)						
Complete response	19 (22.6)	41 (48.8)	0.009*	36 (42.9)	24 (28.6)	<0.001*
Refractory/progression of disease	15 (17.9)	9 (10.7)		17 (20.2)	7 (8.3)	
Relapsing status (64 patients)						
Relapsed	6 (9.4)	5 (7.8)	0.047*	3 (4.7)	8 (12.5)	0.008*
Not relapsed	13 (20.3)	40 (62.5)		37 (57.8)	16 (25)	

PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index. Data are expressed as numbers (%) (Significant).*

Table 4: Outcomes of lymphoma regarding the studied indexes

Parameter	Overall survival		Relapse free survival	
	OS time in months [range]	p-value	RFS time in months [range]	p-value
Overall	18.3 [4-42]		11.6 [1-37]	
PNI				
Low-group (≤ 50)	8 [4-34]	<0.001*	6 [1-30]	<0.001*
High-group (>50)	23 [6-42]		17 [3-37]	
SII				
Low-group (≤410)	23 [6-42]	<0.001*	17.5 [2-37]	0.001*
High-group (>410)	12 [4.-30]		8 [1-22]	

CI: Confidence interval; OS: Overall survival; RFS: Relapse-free survival; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index. Data are expressed as median [Min-Max] (Significant).*

Table 5: Univariate analysis of variable affecting the outcome

Covariate	Overall survival		Relapse free survival	
	Univariate analysis		Univariate analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (>60 years)	2.9 (1.2-7.2)	0.015*	1.2 (0.3-4.5)	0.79
Sex (Male)	0.5 (0.2-1.25)	0.13	0.69 (0.2-2.2)	0.55
Comorbidites	1.9 (0.8-4.65)	0.15	1.8 (0.6-6.1)	0.3
ECOG (≥1)	3.1 (1.3-7.7)	0.013*	3.4 (1-11.4)	0.04*
LDH	2.3 (0.99-5.3)	0.053	0.7 (0.2-2.1)	0.53
Extra-nodal site	3.7 (1.5-9)	0.004*	1.5 (0.3-6.7)	0.63
Bulky sites	3.3 (1.4-8.2)	0.009*	1.1(0.13-8.5)	0.95
B symptoms	3.32 (1.3-8.3)	0.01*	1.8 (0.6-6.2)	0.29
Staging (3&4)	34 (0.5-227)	0.09	2.4 (0.5-11.4)	0.26
IPI (High)	2.5 (1.4-4.5)	0.002*	1.17 (0.5-2.6)	0.69
NCCCN-IPI (High)	3.6 (1.6-8.1)	0.002*	1.5 (0.6-3.9)	0.44
PNI (>50)	0.08 (0.03-0.25)	<0.001*	0.14 (0.04-0.48)	0.002*
SII (>410)	32.2 (4.2-243)	0.001*	14.8 (3.1-72.7)	0.001*

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; IPI: International Prognostic Index; NCCCN: National Comprehensive Cancer Network; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.
(Significant).*

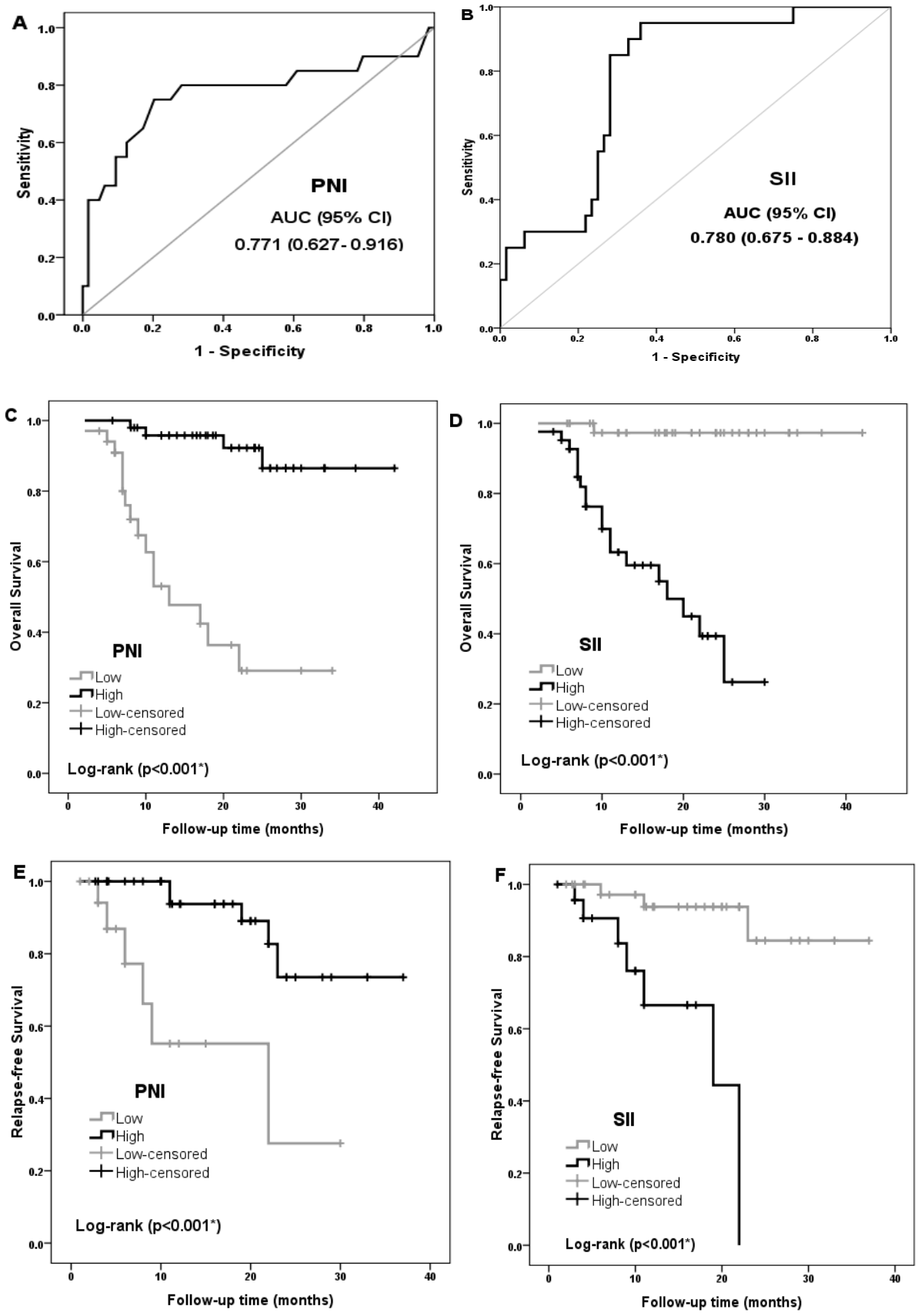

Figure 1: A. ROC curve of PNI; B. ROC curve of SII; C. Overall survival (OS) in relation to PNI; **D.** Overall survival (OS) in relation to SII; **E.** Relapse-free survival (PFS) in relation to PNI; **F.** Relapse-free survival (PFS) in relation to SII.

*ROC: Receiver operative characteristics; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index. *: Significant*

DISCUSSION

The most prevalent lymphoid neoplasm in adults is diffuse large B-cell lymphoma (DLBCL). It constitutes the most prevalent NHL subtype in Egypt [2]. Tumor growth and inflammation are intimately related [10]. Inflammation markers, such as the pretreatment neutrophil-lymphocyte ratio (NLR) [17] and platelet-lymphocyte ratio (PLR) [18], have been shown in numerous studies published in recent years to play a significant role in influencing the outcomes of DLBCL patients. Blood biomarkers are also less expensive and simpler to collect than molecular genetic indicators.

In several solid malignancies, including pancreatic cancer [19], breast cancer [20], lung cancer [21], and gastrointestinal cancer [22], a high systemic immune-inflammation index (SII), which is related to neutrophil, platelet, and lymphocyte counts, has been reported to be a poor prognostic indicator.

The nutritional state of individuals with various solid tumors is also strongly correlated with their clinical outcomes. Additionally, it has been established that the Prognostic Nutritional Index (PNI) is a helpful prognostic indicator in many malignancies, including esophageal carcinoma and osteosarcoma [24].

No matter the location or origin of the tumor, recent studies have shown that PNI can be utilized to predict the clinical outcomes of patients with various malignant tumors [26], [27]. The predictive usefulness of PNI for DLBCL has been the subject of various subjects, although the findings were mixed and conflicting [28, 29].

The link between PNI, SII, and clinical outcomes in patients with DLBCL treated with RCHOP has not been established despite mounting evidence that the SII and PNI, which can reflect systemic inflammation and nutritional statuses, can reliably predict cancer patient prognosis.

In this investigation, we assessed the OS, RFS, and CR rates in DLBCL treated with R-CHOP, the clinical outcomes, and the impact of pretreatment PNI and SII as prognostic variables.

The median follow-up time was 13 months, the median overall survival (OS) was 18.3 months, and the median relapse-free survival (RFS) was 11.6 months. Using the ROC curve, we also evaluated the ideal cut-off values for PNI and SII to predict OS. We separated the patients into low and high groups based on these cut-off values. Analysis of correlations between PNI and SII was unable to find any.

The ROC curve's PNI cut-off value in our study was 50, roughly in line with other studies findings [28, 29]. The cut-off value for SII in our patients was 410, which was higher than Kim's and colleagues' [31] cut-off value and lower than the Chinese group's value. The disease's unique characteristics in Egypt, including several etiological and biological factors, may cause these variances. Additionally, the high seroprevalence of hepatitis C and B virus (33%), as well as probable chronic liver disease, may have had an impact on baseline serum albumin and blood counts.

Our findings showed higher PNI and lower SII were associated with higher complete remission rates (CR). These results provide evidence that PNI and SII can predict chemosensitivity in DLBCL.

In the multivariate analysis, a high PNI was independently associated with better OS and RFS. These results are consistent with earlier studies assessing the impact of PNI in lymphoma patients. A group of Croatian researchers found that the PNI can predict long-term survival outcomes in DLBCL patients. [32] In a Chinese cohort by Yu et al. PNI failed to predict the survival of DLBCL cases treated with RCHOP [28]. In a Korean experience of Go et al. [33], along with IPI and muscle mass loss, PNI was an independent predictor of overall survival in DLBCL patients treated with a rituximab-based regimen. Based on seven studies with a total number of 1311 DLBCL patients, mainly Asian, a meta-analysis showed that low PNI was correlated to poor OS and poor PFS [34].

On the other hand, low SII was significantly predictive of better RFS and OS outcomes. These observations are coherent with the results reported by a Chinese group that assessed SII before treatment. They enrolled 28 patients with testicular DLBCL and found that pretreatment SII was a negative prognostic factor for PFS [35]. Later, in a larger cohort, Wang et al. reported that SII, older age, HBsAg positive, and IPI were the independent prognostic factors for DLBCL patients treated with chemoimmunotherapy in their multivariate analysis [36].

The findings mentioned above showed how PNI and SII have a prognostic value in relation to RFS and OS in an Egyptian cohort of DLBCL patients receiving chemoimmunotherapy.

This study had several limitations. First, the size of our cohort placed constraints on our ability to generate more findings. Second, pathologic aspects of our cohort, such as cell-of-origin subtype, gene expression profiling, and comprehensive evaluation of small-molecule metabolites, were not systematically examined. To more clearly understand the predictive usefulness of PNI and SII in DLBCL in real life,

additional large-scale and well-designed research using both clinical and molecular biomarkers is required.

CONCLUSIONS

A growing body of evidence demonstrates the value of pretreatment PNI and SII as simple prognostic indicators in DLBCL patients receiving RCHOP. Both are also easily accessible and might be employed in designing the next clinical trials for DLBCL patients. To acquire consistent PNI and SII cut-offs and precisely forecast the prognosis of DLBCL patients, larger multi-center clinical trials are necessary.

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