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Review Article

An overview of the correlation between IPI and prognosis in primary breast lymphoma

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Abstract: Primary breast lymphoma (PBL), with diffuse large B-cell lymphoma (DLBCL) as the most histopathological type, is a rare disease with a poor prognosis. The International Prognostic Index (IPI) is an important clinical characteristic for risk stratification of PBL patients with different prognoses. However, the prognostic value of the IPI in PBL is controversial and needs to be refined. In this review, we described the clinical characteristics, pathogenesis, and treatment of PBL, with emphasis on the prognostic value of the IPI, its updated versions and IPIs for certain subtypes. A total of 9 types of IPIs were presented. In addition, the key issues with the various treatment modalities available were addressed, as well as the role of rituximab in therapy. We also summarized the current evidence and future challenges facing other types of prognostic indices. In particular, prospective clinical studies of treatment are rare, and the available data were mainly obtained from retrospective case series that included a small number of patients. Therefore, our conclusions and recommendations cannot serve as formal guidelines. However, this review attempts to provide an unbiased analysis of published data to provide clinicians with useful assistance in the treatment of this uncommon form of extranodal lymphoma.

Keywords: Primary breast lymphoma (PBL), international prognostic index (IPI), prognostic index, rituximab

Introduction

Primary breast lymphoma (PBL) is an extra lymph node lymphoma with a low incidence. Relevant statistical results show that it accounts for about 1% of all Non Hodgkin's lymphoma (NHL) [1-3]. This type of lymphoma rarely occurs in the male population [4]. The main subtype of PBL is diffuse large B-cell lymphoma (DLBCL) [1, 5, 6], which is relatively aggressive, and has a very negative impact on the prognosis of patients [1, 6].

The International Prognostic Index (IPI) is widely used to evaluate the prognosis of patients with aggressive lymphoma [7]. Different methods can be selected when treating DLBCL patients. The commonly used one is rituximab plus CHOP therapy, and the prognosis of patients obviously improved after treatment. The ability of the IPI to stratify prognosis in patients receiving immunochemotherapy was severely reduced. In the era of immunochemotherapy, the cure rate of patients has increased by nearly 15% [8, 9]. However, 1/3 of the patients died of refractory disease or relapsed, the survival rate of patients at high risk was greater than 50% [10]. Better stratification strategies for these patients and methods for differentiating them in addition to the original subgroup stratification method are needed.

Therefore, updated versions of IPI, such as the revised-IPI (R-IPI), the NCCN-IPI, and age-adjusted IPI (aaIPI), were established.

Clinically, IPI scores are widely used as a prognostic tool for risk stratification for PBL. However, due to the rarity of PBL and the lack of large-scale studies, the predictive value of IPI in PBL is controversial, especially in the rituximab era. This review article overviews the impor-

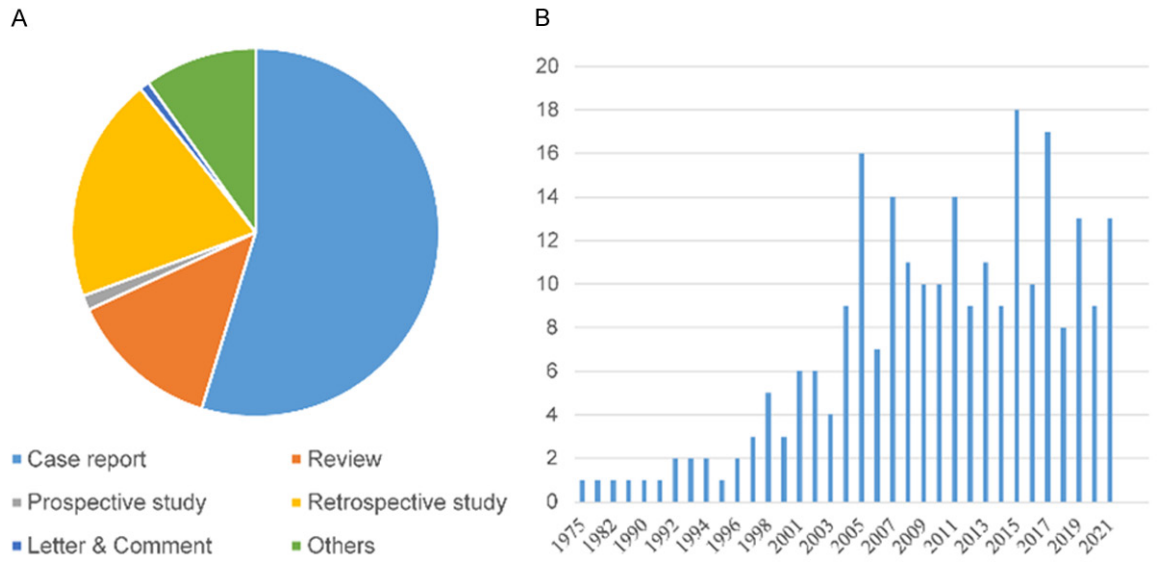

Figure 1. A review of literature on primary breast lymphoma published between January 1975 and December 2021. A. Literature published on topics pertaining to primary breast lymphoma. B. Number of published articles in each year. A search of published papers between January 1975 and December 2021 was performed using the PubMed and Web of Science databases. The terms "primary breast lymphoma" and "primary lymphoma of the breast" were used as keywords for database searches. Nonrelated studies and studies not published in English were excluded from this analysis.

tance of the IPI and its adjusted versions for PBL in the published clinical research literature.

A search of papers published between January 1975 and June 2020 was conducted based on the PubMed and Web of Science databases. In the searching process, the terms "(primary breast lymphoma [Title]) OR (PBL [Title])" were used as keywords. Nonrelated studies and studies not published in English were excluded. A total of 234 published pieces of literature were found. Among these, 97 were case reports; 32 were reviews, meta-analyses, systematic reviews, letters, and comments; and 52 were clinical studies (**Figure 1**). To explore the application of IPI, a total of 25 clinical studies containing information on IPI were summarized.

Overview of PBL

The clinical and imaging features of PBL

At present, there has no specific index to distinguish PBL from breast cancer. According to a large amount of clinical experience, the most important feature of breast lymphoma is painless mass (61% of cases), which is about 4 cm in diameter [1, 11]. Approximately 40% of patients may exhibit palpable lymph nodes [12]. Bilateral breast involvement was not common in approximately 11% of cases [11, 13-15]. B symptoms, such as fever, weight loss are rare and usually indicate disseminated disease [16, 17].

The imaging characteristic of PBL is indistinguishable from other breast malignancies; therefore, a specific diagnosis cannot be made solely based on the findings of these modalities, for example, ultrasound, mammography and MRI, each of which has a certain scope of application. The investigation results show that at present, [18F] fluorodeoxyglucose (FDG) and CT positron emission tomography (18F-FDG PET/CT) are often used in the field of PBL disease evaluation. In addition, tumor staging and invasiveness can also be determined by this technology, which has certain application value in the evaluation of efficacy. According to previous experience, the data obtained from baseline 18F-FDG PET/CT can be used to evaluate the prognosis of PBL patients [18-20]. Zhao studied the risk level of PBL patients and combined TMTV and β2-microglobulin set up a model and made an empirical analysis on the predictive value of the model [18].

Diagnosis and staging

The diagnosis of PBL was established according to cytologic and histopathologic testing. The diagnosis still depends on a puncture or postoperative pathological examination, and the specific classification is finally confirmed by immunohistochemistry. According to the definition of Wiseman [21], the clinical staging of PBL is mainly Ann Arbor IE or IIE, and other relevant indicators include ipsilateral supraclavicular lymph node involvement. The relevant statistical results show that the prognosis of bilateral PBL is generally worse, so such pathology is generally classified as stage IV in most studies [1, 2, 12, 22, 23].

Pathogenesis

The origin of lymphocytes leading to lymphoma is still uncertain; According to the results of previous experimental studies, it is inferred that these tumors are mainly caused by the stimulation of mucosa associated lymphoid tissue and inflammatory lymph nodes [24, 25].

Relation to sex hormones

PBL mainly occurs in women, while male cases are occasionally reported, suggesting that sex hormones may be related to the pathogenesis of PBL. Bilateral breast involvement and Burkitt-type lymphoma are often observed in younger pregnancy patients, suggesting a hormonal correlation [26, 27]. Positive estrogen receptor (ER) staining has been noted in PBL tissue samples [28]. Aviv et al. [29] once reported a case of MALT in the breast with positive progesterone receptor (PR) but negative ER results. ER-beta (ERβ) isoform expression in human lymphoma cell lines is abundant, especially in germinal center (GC) lymphocytes and the follicular mantle zone. Additionally, ER-alpha (ERα) is expressed only in activated GCs but not in follicular cells [30, 31].

Lymphoma homing

The selective homing of lymphoma cells may explain the high relapse rate in the contralateral breast, which may be mediated by tissue chemoattractants [32]. The mechanism of lymphoma homing in PBL has yet to be uncovered.

Relation to immune system disease

Some case reports of PBL with concomitant immune system disease have been reported [33, 34]. The three most common systemic autoimmune diseases, Sjögren's syndrome (SS), rheumatoid arthritis (RA), are related to higher risk of lymphoma [35, 36]. Autoimmune B cells continuously stimulated by immune complexes is very important. In the pooled cohort study by Setoguchi, the standardized incidence ratios for non-Hodgkin's lymphoma in RA were more than double those in the general population [37].

Subtype of PBL

DLBCL is the most common histologic subtype of PBL (comprising 40%-80%) [17, 38-40]. Marginal zone lymphoma (MZL) (9%-28%) are the most frequent [17, 41-43]. Follicular lymphoma (FL) (10%-19%) [41, 42, 44] and Burkitt lymphoma (1%-5%) [45, 46] are also identified [17]. Other rarer (each < 1%) histological types include small lymphocytic lymphoma [47], mantle cell lymphoma [48], plasmablastic lymphoma [49], peripheral T-cell lymphoma, and Hodgkin lymphoma [50].

Overview of the IPI and updated versions

The IPI score

Factors involved in IPI scoring mainly include age, performance status of ECOG, basic status, number of extranodal sites, LDH level, etc. [51]. Patients are grouped based on the number of risk factors, including low risk group, medium risk group and high risk group. The more risk factors, the higher the risk level. The 5-year OS rates were 26%, 43%, 51%, and 73%. Among these 25 clinical studies, 22 studies used the IPI scores.

There is a negative correlation between IPI and survival outcome (IPI). If the score of IPI is large, PFS and survival will be more affected. Some scholars found that some IPI components were not related to DLBCL treated with rituximab, so IPI should be revised appropriately [52].

The R-IPI score

So the improved IPI, the R-IPI, was set by Sehn [53]. For R-IPI, the IPI scores were redistributed

to form three groups, and this score predicts clinical outcomes better than the IPI.

The R-IPI using the same risk factors as the IPI. A score of 0 indicates the very good-risk group, with a 4-year progression-free survival (PFS) of 94% and an overall survival (OS) of 94%; a score of 1-2 indicates the good-risk group; and a score of 3-5 indicates the poor-risk group (4-year PFS 53%, OS 55%) ($P < 0.001$).

The NCCN-IPI score

To identify subgroups of patients with a 5-year OS of less than 50%, an enhanced IPI scoring system for those with newly diagnosed DLBCL therapied with R-CHOP was constructed rely on the NCCN-IPI.

The comparative analysis shows that the risk factors of NCCN-IPI and IPI/R-IPI are basically the same. However, the scores of each risk factor in the former were redefined, and the age and LDH level were evaluated in different ways. The patients were divided into four groups based on the results obtained.

Unlike the number in the IPI scoring system, the NCCN-IPI scoring system rates the involvement of bone marrow, or extranodal lung lesions as 1 point. The NCCN-IPI total score is 0-8: score of 0-1 indicates the low-risk group; 2-3 indicates the low-intermediate-risk group; 4-5 indicates the high-intermediate-risk group; and 6-8 indicates the high-risk group.

The age-adjusted IPI (aaIPI)

The aaIPI was developed for patients aged ≤ 60 years. It involves 3 adverse prognostic factors, including stage III-IV, high LDH levels, and ECOG PS score ≥ 2. A score of 0 is considered low risk, 1 corresponding to low risk, 2 corresponding to high risk, 3 corresponding to high risk. The study by Zhang et al. [54] investigated risk stratification based on aaIPI scores. aaIPI-based risk stratification was strong related to PFS and OS ($P < 0.05$).

The GELTAMO-IPI

The GELTAMO-IPI was proposed in 2017 by Montalban et al. [55] Age and ECOG status were further subdivided, β2-MG concentration was added as one of the evaluation indicators, and extranodal lesions and LDH levels were removed. Unlike the NCCN-IPI and IPI, GELTAMO-IPI can be used to screen real high-risk groups. Its predictive efficacy is not influenced by extranodal location or the intensity of the treatment regimen. There are few relevant studies of the GELTAMO-IPI, and this approach must be further explored.

The central nervous system (CNS)-IPI

The recurrence of the central nervous system will have a very negative impact on the prognosis of patients. Research has found that there are many factors related to the risk of CNS recurrence, such as LDH level, the number of extranodal sites involved, and ECOG PS greater than 1. Hosein [16] showed that the risk of CNS recurrence was significantly increased with stage II E disease and higher IPI score, but no statistical significance was reached.

Schmitz et al. [56] developed a CNS risk model, CNS-IPI, for patients with CNS relapse. Factors considered in determining the overall prognosis of CNS mainly include renal involvement, advanced age, high LDH level, ECOG PS > 1, etc. Yhim's [23] research results show that the CNS IPI index has no application value when stratifying patients according to CNS recurrence risk. On the basis of a large number of empirical statistical analysis, the German GHLSG team proposed a highly referential CNS-IPI score to identify high-risk patients [56].

The IPIs and subtypes of PBL

Primary breast DLBCL (PB-DLBCL)

PB-DLBCL is a kind of common type of PBL. It has a different pattern of relapse from nodal DLBCL, as the relapse of ipsilateral or contralateral breast and the bone marrow, lung or pleura, and central nervous system (CNS), were reported with high frequency compared to a would expect for DLBCL [2, 16, 57]. The association of IPI scores and survival prognosis in PBL is controversial. The IPI can be seemed as a significant prognostic index for OS, PFS, and CSS ($P < 0.001$) in the study by Ryan et al. [1], Ludmir et al. [58, 59], and Aviles et al. [60] demonstrated no significant relationship between PFS and IPI ($P = 0.32$). IPI scores were very important risk factors in the multivariate analysis for PFS and OS in research of Hu [61],

Luo et al. [39], Niitsu et al. [62], Hosein et al. [16], Shao [63].

The IPIs and other subtypes of PBL

For certain subtypes, however, such as MALT, FL, and MCL, the MALT lymphoma prognostic index (MALT-IPI), FL prognostic index (FLIPI) [64], and MCL prognostic index (MIPI) [65], have been developed that can be used to more precisely distinguish between various prognostic groups.

Primary breast MALT lymphoma (PB-MALT)

MALT lymphoma is a kind of indolent lymphoma. The effect of traditional tumor therapy is not obvious, and the improvement of its survival period is limited; In the process of managing early PB-MZL, close observation is required, but at present, prospective research in this field is relatively lacking.

Thioblemont et al. [66] applied relevant indicators (age ≥ 70 years, Anaborg III, high LDH) and formulated relevant evaluation criteria when determining the recurrence risk of such patients. The results obtained are of important reference value. However, Ludmir et al. [58] did not observe any predictive value for MALT-IPI, consistent with previous reports on PB-MALT lymphoma by Martinelli et al. [41].

Primary breast follicular lymphoma (PB-FL)

The incidence of FL is very common type of NHL, approximately accounting for 70% of all indolent lymphomas [67]. PB-FL is a rare entity described in only 14 case series [68-81] and relevant researches with a limited number of cases [41, 82]. Three male patients with PB-FL issues were reported [70, 73, 78]. Six of these cases were related to the synchronous incidence of lymphoma [68, 76, 79, 80]. Most patients with FL of the breast who present with early-stage local disease respond very well to definitive radiation therapy [41]. The addition of rituximab obviously reduced relapse risk and increase overall survival, although not statistically significant [41].

Solal-Coligny et al. [64] established the FLIPI to adapt to the era of rituximab, and then the same working group developed the FLIPI-2 [83] based on a prospective study in 2009, both of which have improved the ability to discriminate high-risk patients.

In the IELSG study [41], the FLIPI score was assessed in on 54 patients with FL: 24 exhibit low score, while three presented an mean score. Regarding the IPI score, 18 patients were at low (0-1) risk, and 2 were at low-intermediate (2) risk. In the univariate analysis, FLIPI was a significant risk factor of PFS (P = 0.03) but not OS (P = 0.14).

Primary breast mantle cell lymphoma (PB-MCL)

MCL is a subtype of small B-cell lymphoma. PB-MCL is extremely rare, and only 5 cases have been reported [48, 84-87]. There are limited data relevant to the prognosis in PB-MCL. Most patients were treated identically to those with systemic MCL using chemoimmunotherapy protocols.

The current prognostic assessment system for MCL is the MIPI system, including evaluations of age, ECOG score, LDH level, and white blood cell level (WBC). Risk stratification was performed according to the score, namely, low risk (0-3), intermediate risk (4-5), and high risk (6-11). The higher the risk stratification, the shorter the median survival time. In addition, Ki-67 is a prognostic factor for classic MCL. The higher the content of Ki-67 is, the higher the proliferation index of the tumor and the worse the patient's prognosis. Therefore, MIPI combined with Ki-67 assessment can be used to classify patients into low-risk groups, low-intermediate risk, medium-high risk, and high-risk. No MIPI-related studies of PB-MCL were found.

The timeline of the development of the IPI and updated versions are shown in **Figure 2**, and the association between these IPIs mentioned above is shown in **Figure 3**. The comparison of IPIs is shown in **Table 1**.

The IPIs and treatment

There is no unified and clear guideline for the treatment of PBL patients. However, in clinical treatment, the main method is immunochemotherapy combined with radiotherapy. A large number of statistical studies have found that surgical treatment will not significantly affect

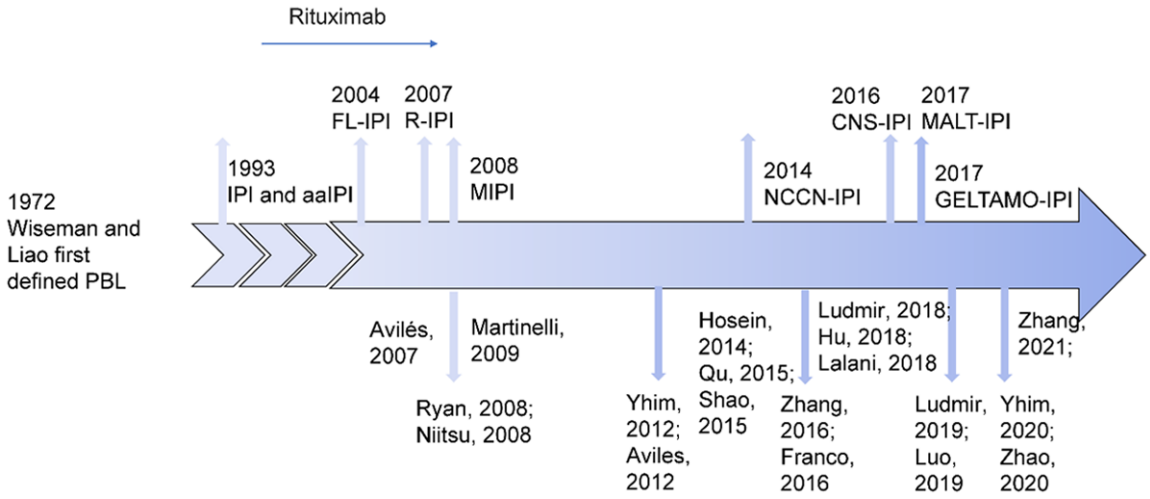

Figure 2. The timeline of the development of IPIs and IPI-related studies.

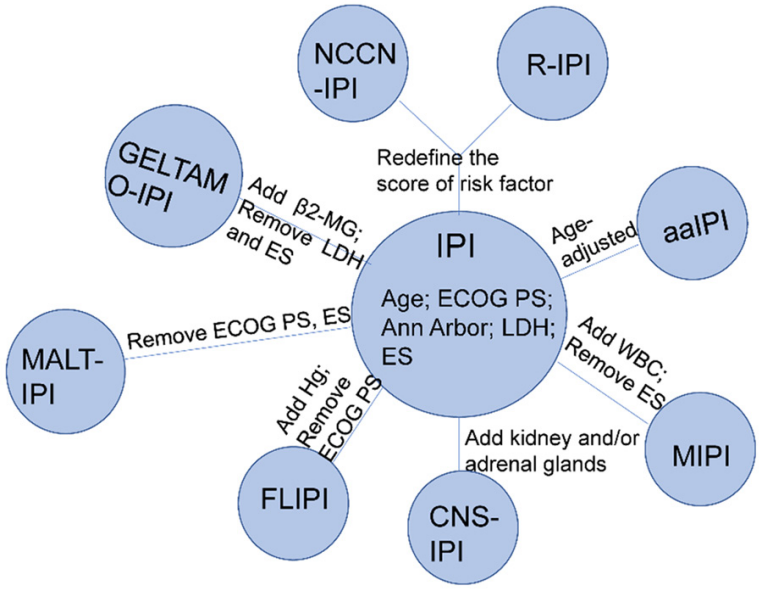

Figure 3. Schematic illustration of the association between IPIs.

the long-term prognosis of such patients, so it is not the main treatment mode. The biopsy can be performed with surgery, but it is not used for treatment. Jennings et al. [88] performed mastectomy in 156 patients (33.5%), and found that there was a correlation between surgery and OS (P = 0.055). In the IELSG studies [1, 41] of 278 patients, approximately two-thirds underwent further surgery. For patients undergoing mastectomy, whether the operation is performed or not will not significantly affect their PFS or OS. Some scholars have studied PBL patients with different risk levels and obtained the same results. Comparative analysis found that patients with surgical treatment were more prone to relapse [1, 41].

The IPIs and rituximab

As in nodal forms of DLBCL, rituximab plus CHOP (R-CHOP) therapy has been applied in the treatment of PB-DLBCL. The multicenter study by Hu et al. [61] confirmed that rituximab can significantly reduce the cumulative risk of progression or relapse in PB-DLBCL patients. In contrast, another multicenter study from 8 US academic centers [16] and 16 Korean institutions [89] found that rituximab use was not related to longer survival. In the prospective study by Avilés et al. [60], the addition of rituximab can't enhance the prognosis of DLBCL-PB. These conflicting results were all stratified by IPI scores, and the application of rituximab was not affected by the IPI scores. Ludmir et al. [58] reported high rates of disease response with rituximab. The application of rituximab to different IPI groups was not affected by the MALT-IPI scores. It is important to identify patients with high recurrence risk and carry out targeted treatment to improve the prognosis of such patients. Therefore, it is

Table 1. Comparison of different versions of IPIs

		NCCN-IPI	IPI	R-IPI	aaIPI	GELTAMO-IPI	FLIPI	MALT-IPI	MIPI
Age	≤ 40	0	0	0	Not included	0	0	< 70 0	< 50 0
	41-60	1						≥ 70 1	50-59 1
	61-75	2	1	1		1	1		60-69 2-4
	> 75	3							
ECOG PS	≤ 1	0	0	0	0	0	Not included		0
	≥ 2	1	1	1	1	1			2
Ann Arbor	I-II	0	0	0	0	0	0	0	Not included
	III-IV	1	1	1	1	1	1	1	
LDH	Normal	0	0	0	0	0	0	0	< 0.67 0
	Increased	1	1	1	1	1	1	1	0.67-0.99 1 1.0-1.49 2
β2-MG	Normal		Not included		Not included	0	Not included		Not included
	Increased					1			
Extranodal sites	0	0	0	0		Not included	lymph node involvement > 4 0		Not included
	1								
	≥ 2	1	1	1			≤ 4 1		
WBC (10^9/L)	< 6.7			Not included			Not included		0
	6.7-10								1
	≥ 10								2
Hg (g/dL)	< 12						1	Not included	
	≥ 12						0		
Groups	Low-risk	0-1	0-1	very good risk 0	0	0	0-1	0	0-3
	Intermediate-low risk	2-3	2	good risk 1-2	1	1-3			
	Medium-high risk	4-5	3	poor risk 3-5	2	4	2	1	4-5
	High risk	6-8	4-5		3	5-7	3	> 1	6-11

IPI, International Prognostic Index; NCCN-IPI, National Comprehensive; Cancer Network IPI; R-IPI, Revised IPI; aaIPI, age-adjusted IPI; FLIPI, Follicular Lymphoma IPI; MALT IPI, mucosa-associated lymphoid tissue lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; β2-MG, β2-microglobulin; WBC, white blood cell.

necessary to pay attention to this and take appropriate methods for accurate detection during treatment.

The IPIs and RT

The benefits of radiotherapy for PBL patients receiving rituximab-containing regimens remain controversial. In the retrospective international study by IELSG, RT obviously reduced ipsilateral progression ($P = 0.29$) [1]. Jeanneret-Sozzi et al. [90] also confirmed that the use of RT was a factor contributing to favorable prognosis in PBL by multivariate analysis in their multicenter Rare Cancer Network study. However, Yhim et al. [23] omitted routine consolidative radiotherapy in their phase 2 prospective study (NCT01448096) due to its conflicting results on survival outcomes. In this study, radiotherapy was only permitted if patients had a bulky disease. Among 33 patients in this study, only one patient had ipsilateral breast relapse and received involved-field radiotherapy. This study argued for the need for RT in primary PBL patients, given the substantial risk of subsequent breast cancer (3 years, 10.2%).

There is currently no clear association in terms of the relationship between the IPI scores and RT. In the study by Ryan et al. [1] and Ludmir et al. [59] ($P = 0.37$), the RT was negatively related to the IPI. Zhang et al. [54] suggested that breast irradiation is associated with improved OS and PFS, justifying its consideration based on the age-adjusted IPI.

However, in the study by Hu et al. [61], there was no obvious difference in IPI between patients treated with and without RT. Martinelli et al. [41] reported the application of FLIPI in 36 PB-FL patients, and most patients received RT.

The basic information of the studies, including details on IPI, is shown in **Table 2**.

Other prognostic factors

Due to the clinical and biological heterogeneity of PBL, related experimental studies have found that the mutation of inflammatory factor gene plays an important role in the pathological changes of lymphoma. The prognostic value of the IPI and other versions is limited, and more comprehensive models were established (**Figure 4**).

As all the IPIs are based on pretreatment characteristics, because of the heterogeneity of the tumor, the treatment results of the same IPI patients may be significantly different due to individual factors after the same chemotherapy. Some scholars have carried out relevant basic research and established corresponding gene predictors, such as cell origin, MYC and BCL2. Aishi's prediction shows certain application value [91]; High MIB-1 index [92] generally indicates poor prognosis, but its application value is not very clear, and large sample test is required. The reduction of cost and the wide application of high-throughput technology are of great significance for deepening the understanding of the pathological mechanism of DLBCL and PBL in lymph nodes. Taniguchi et al. [93] found that the proportion of MYD88 and CD79B mutations in PB-DLBCL patients increased significantly, which can be used for pathological interpretation. Franco et al. [94] designed a targeted sequencing panel of 38 genes in 17 patients with PB-DLBCL. This finding provides a new perspective for targeted biomarkers and prognostic indices. Su et al. [95] selected 68 patients with PB-DLBCL as subjects, detected the protein expression of relevant biomarkers in their lymph tissues, and determined the proteins with significant differences in expression levels. Survival analysis results indicate that the three clusters have important predictive value.

Since tumor progression involves interactions with inflammatory response molecules in the tumor microenvironment, inflammatory factor gene polymorphism can significantly affect the risk of lymphoma, and also determine the prognosis of such patients [96]. The predictive model comprising genetic alterations and clinical variables should be further investigated. Some studies [38, 62] indicated that increased microvessel density, soluble interleukin 2 receptor level, or serum β2-microglobulin levels could be used as indicators of poor prognosis of PBL. However, these prognostic indicators have not been widely recognized. PET/CT is important for staging lymphoma; there is growing evidence of the predictive value of PET/CT data for PBL.

Conclusion

This review summarizes the application of IPI prognostic scoring systems and revised ver-

Table 2. Basic information of 25 studies including information on IPI

Author, year	N	FU (Year)	Age		IPI		B symptoms		5-year OS	5-year PFS	Treatment (N)			
			< 60	≥ 60	0-1	2-5	Absent	Present			Surgery	R+ChT	ChT	RT
Ryan, 2008 [1]	204	5.5	81	123	129	37	195	9	46%	36%	9	0	143	130
Ludmir, 2019 [58]	11	8	62 (42-75)		5	6	11	0	NA	NA	1	NA	NA	8
Hu, 2018 [61]	108	3.2	47 (16-85)		78	13	103	5	77.3%	61.2%	21	66	108	39
Zhang, 2021 [54]	36	2.8	18	11	3	15	14	15	NA	NA	0	8	8	14
Luo, 2019 [39]	46	3.4	28	18	33	13	44	2	36.2%	29.1%	38	16	46	12
Ludmir, 2018 [59]	25	4.5	55 (26-83)		16	6	24	1	71.9%	42.4%	5	16	24	13
Niitsu, 2008 [62]	30	5.5	57 (24-77)		23	7	27	3	87.0%	77.0%	NA	11	30	18
Yhim, 2020* [23]	33	3.8	50 (29-75)		28	5	31	2	93.5%	81.3%	NA	32	32	NA
Zhang, 2016 [97]	24	5.0	50 (24-69)		19	5	23	1	78.9%	79.2%	17	10	23	12
Hosein, 2014 [16]	76	4.5	62 (17-87)		54	22	74	2	75.0%	66.0%	NA	47	65	48
Ou, 2015 [98]	23	3.8	16	5	21	2	22	1	57.1%	57.1%	3	7	19	1
Zhao, 2020 [18]	64	5	51	13	54	5	53	11	73.4%	62.5%	29	39	59	39
Zhang, 2017 [3]	29	5.5	50 (24-69)		21	8	27	2	78.1%	78.4%	21	11	27	13
Shao, 2015 [63]	30	2.7	45 (18-74)		17	13	25	5	48.0%	32.0%	NA	13	24	5
Avilés, 2007* [99]	32	5.4	16	16	32	0	NA	NA	63.0%	75.0%	NA	0	32	NA
Aviles, 2012 [60]	104	NA	NA	NA	104	0	NA	NA	52.0%	66.0%	NA	49	55	0
Martinelli, 2009 [41]	60	4	25	35	36	NA	56	4	92.0%	56.0%	40	NA	25	36
Yhim, 2012 [100]	26	2.9	56 (21-79)		20	5	24	1	82.2%	70.0%	NA	6	25	10
Liu, 2020 [101]	370	5.7	114	256	NA	NA	NA	NA	81.2%	95.4%	71	NA	63	142
Lalani, 2018 [102]	35	5.8	66 (35-86)		NA	NA	31	4	70.0%	NA	15	10	15	30
Franco, 2016 [103]	55	4.7	28	25	NA	NA	51	2	76.0%	73.0%	14	39	35	20
Radkan, 2014 [104]	28	NA	67.5 (35-95)		NA	NA	NA	NA	82.0%	75.0%	17	NA	15	16
Jeanneret-Sozzi, 2008 [90]	84	4.7	42	12	NA	NA	NA	NA	53.0%	59.0%	21	0	59	51
Lin, 2006 [105]	32	6.3	43 (22-76)		NA	NA	NA	NA	63.9%	58.6%	32	NA	28	20
Jennings, 2007 [88]	465	4.0	54 (17-95)		NA	NA	NA	NA	NA	44.5%	156	0	323	218

*Prospective studies. FU, follow-up; IPI, International Prognostic Index; PFS, progression-free survival; OS, overall survival; ChT, chemotherapy; R, rituximab; NA, not available.

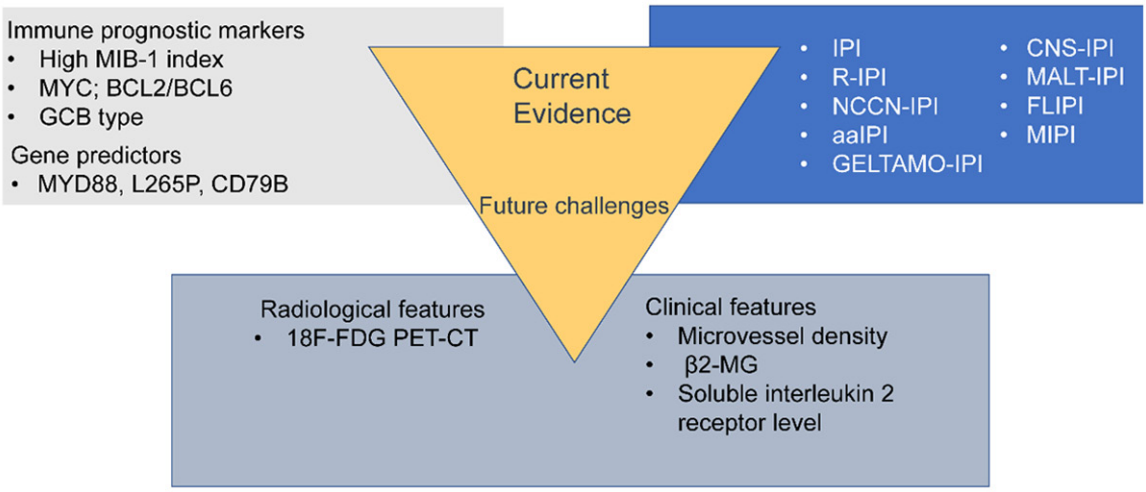

Figure 4. Summary of current evidence and future challenges of prognostic indices of PBL.

sions to the evaluation of PBL, a relatively rare malignant lymphoma of the breast. Under the situation that rituximab is widely used, the predictive value of IPI is also significantly affected. Therefore, it is necessary to conduct in-depth research, establish a more efficient prognosis evaluation model, and accurately analyze the recurrence risk and prognosis of such patients. This extensive literature review is benefit for the predictive function of IPI and revised versions of different subtypes of PBL and treatment for clinicians treating patients with this rare disease.

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Disclosure of conflict of interest

None.

Abbreviations

PBL, primary breast lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MRI, magnetic resonance imaging; 18F-FDG PET/CT, positron emission tomography (PET) using [18F] fluorodeoxyglucose (FDG) combined with computed tomography (CT); IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-IPI; aaIPI, age-adjusted IPI; R-IPI, revised-IPI; GELTAMO-IPI, Spanish Lymphoma/Autologous Bone Marrow Transplant Working Group-IPI; CNS-IPI, central nervous system-IPI; MALT-IPI, MALT lymphoma prognostic index; MIPI, MCL prognostic index; FLIPI, FL prognostic index; ES, extranodal sites; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; MALT, mucosal-associated lymphoid tissue; ER, estrogen receptor; PR, progesterone receptor; GC, germinal centers; MZL, marginal zone lymphoma; FL, follicular lymphoma; PFS, progression-free survival; OS, overall survival; R-CHOP, rituximab plus CHOP.

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