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Available prognostic models for risk stratification of diffuse large B cell lymphoma patients: a systematic review

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ABSTRACT

The International Prognostic Index (IPI) has been used for risk stratification for a long time in diffuse large B cell lymphoma (DLBCL). Based on new clinical and biological prognostic markers, many new prognostic models have been described. This review aims to present the progress in development and validation of these prognostic models. A comprehensive literature review was performed to identify studies that proposed a new prognostic model in DLBCL.

A total of 38 studies met the inclusion criteria. The IPI, revised IPI (R-IPI), and National Comprehensive Cancer Network (NCCN)-IPI were the most studied prognostic indexes, externally validated and commonly used to compare to other models.

Despite an increasing number of prognostic models have been proposed lately, most of them lack external validation. Further studies, that combine biological and clinical markers with prognostic significance, are needed to determine the optimal prognostic tool for more personalized treatment approach to DLBCL patients.

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphomas (NHL). It is a clinically and biologically heterogeneous disease with a variable course. (Saygin et al., 2017). The most common used tool for prognostication in DLBCL patients still remains the International Prognostic Index (IPI), despite being created in the pre-rituximab era – (about 25 years ago) (Shipp et al., 1993). The prognostic significance of the IPI has been validated in several studies, including those which analysed rituximab-treated patients (Ziepert et al., 2010; Hosoda et al., 2018). However, some of them pointed to a decline in prognostic value of the IPI in the rituximab era (Sehn et al., 2007; Zhou et al., 2014). Moreover, better understanding of lymphoma biology and identification of new molecular markers with potential prognostic significance, has led to multiple attempts to refine the IPI since the beginning of the rituximab era.

On the other hand, new prognostic scores have relatively low adoption in both clinical trials and routine care, possibly due to the absence of validation in patient populations beyond the initial analysed cohort. Prognostic models based on new molecular insights in pathobiology are currently far from routine clinical usage (Melchardt et al., 2015).

Although gene-based predictors have good discrimination ability, when used alone, the IPI remains the most powerful predictor of the clinical outcome of patients with DLBCL (Hong et al., 2013). In fact some of the clinical studies pointed to easily available robust clinical parameters having superior prognostic value compared to molecular markers (Salles et al., 2011; Schmidt-Hansen et al., 2017). Due to all the limitations presented in - recent literature, there is no clear general consensus as to what constitutes a feasible and widely applicable prognostic score that captures lymphoma biology, clinical parameters and host factors such as age and comorbidity, that eventually could guide treatment choice in newly diagnosed DLBCL patients.

This review comprehensively evaluates reported prognostic models in DLBCL, and focuses on those that include combination of at least one clinical and/or laboratory parameter with/without molecular and imaging parameters. Furthermore, special reference is made to the elderly DLBCL patients. So far, this report is the first review that summarises available prognostic models in DLBCL.

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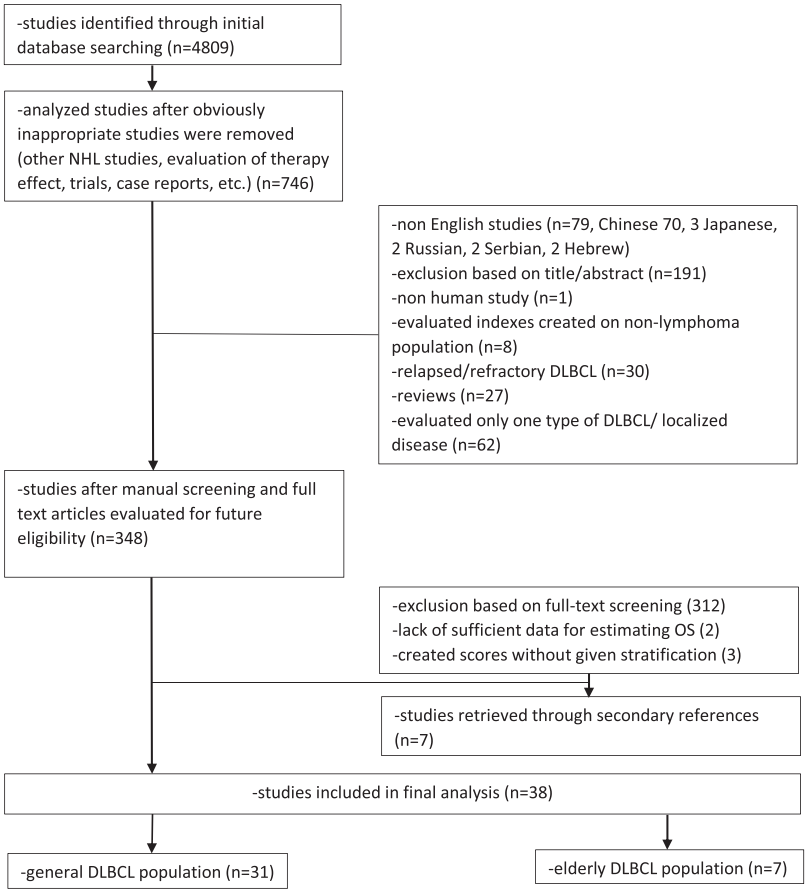

Fig. 1. Shows the selection process of these studies. The involved studies were all published between 1993 and May 2018.

2. Materials and methods

This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (Liberati et al., 2009).

2.1. Search strategy and selection criteria

A literature search was performed through PubMed, and Embase in order to identify all primary research studies available, which have proposed prognostic scores for newly diagnosed DLBCL patients. This search strategy was also performed in order to identify studies that have validated previously proposed scores.

The electronic search was performed by combining Medical Subject Headings (MeSH) and text words, using the following terms: “Lymphoma, Large B-Cell, Diffuse/DLBCL”, “index/indices”, “model”, “score”, “prognosis/prognostic”, “outcome”, “survival”, “validity/validation” and “comparison”. The language was restricted to English. All the studies published between 1993 and May 2018 were included. Additional articles were retrieved through references included in the eligible studies and relevant reviews.

The search was performed independently by two authors (JJ, MM) who screened the initial search results, excluding all obviously irrelevant studies. Then the titles and abstracts of the remaining records were screened, excluding likely irrelevant studies. After examining the full text, relevant studies were included in the final lists. The studies included in the final analysis were checked for availability of relevant data by GT. The final critical appraisal of included relevant studies was performed by (TSL). All authors have approved the final article.

2.2. Selection criteria

The following inclusion criteria were established: (1) all included patients should be newly diagnosed with DLBCL; (2) the study should propose a new index that was created with reference to the population of DLBCL patients (3) the index should contain a combination of at least two parameters, including mandatory clinical/or laboratory parameters with reported risk stratification; (4) the clinical/or laboratory parameters could be combined with imaging and/or molecular prognostic markers; 5) the outcome should be evaluated through overall survival (OS) expressed as a percentage.

Articles were excluded if they (1) were case reports, letters, commentaries, meeting records or review articles; (2) included only patients with one type of DLBCL (e.g. primary central nervous system lymphoma (PCNSL); leg type, primary mediastinal B cell lymphoma (PMBCL), etc.); (3) lacked sufficient data for estimating OS (4) proposed an index based exclusively on histopathological or molecular data; 5) studies that tested models that were created on populations other than lymphoma (e.g. cancer, geriatric patients, etc.); or 6) indexes created on a relapsed/refractory DLBCL population.

2.3. Data extraction

After an initial database search was carried out, each study was screened for eligibility based on the abstract and finally full text. From this, the necessary data for descriptive and quantitative analysis were extracted.

The extracted contents included the first author’s name, index name where given, publication year, parameters included in the search, risk categories, number of patients per group of new index (where available) expressed as a percentage, date of recruitment, inclusion and

exclusion criteria, sampling type, statistics, median age of analysed patients, follow-up duration, and OS. If the OS was not reported directly, data were extracted from the survival curve published in the article and then percentages were estimated by using GetData Graph Digitizer 2.26. Where available 5-year OS was preferably reported.

3. Results

According to the initial search strategy, a total of 4809 potentially relevant articles were recognised in PubMed, and Embase. After a browse of the titles and abstracts, non-English studies, non-human studies, evaluated indexes created on non-lymphoma population, relapsed/refractory DLBCL, reviews, studies that evaluated only one type of DLBCL/localized disease, 348 papers were obtained for the full-text. Of them 31 studies were included in the review, along with 7 that were retrieved from secondary references, while the remaining 317 were excluded based on full-text screening, lack of sufficient data for estimating OS, and creation of scores without given stratification (Fig. 1). No unpublished relevant studies were obtained.

A total of 38 studies proposed scores that could be used in the general DLBCL population, of which, 7 proposed models that only evaluated elderly patients. (Fig. 1).

Tables 1 and 2 provide a summary of the mutual parameters that were used in each score in both the general, and elderly DLBCL population, respectively. Table 3 provides a summary of characteristics of each of the included studies. Table 4 gives a summary of statistical methods, median OS, follow up and validation for each study. Table 5 provides a summary of number of studies per each parameter that were used in prognostic model, with given references. All studies were retrospective observational studies. However, there wasn't found clinical trial that proposed a new prognostic model for DLBCL patients.

Stage of the disease, according to Ann Arbor (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Gang et al., 2015; Kong et al., 2016; Xu-Monette et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014; Miura et al., 2017; Liu et al., 2018a; Pardal et al., 2018) and ECOG (Eastern Oncology Cooperative Group) (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Huang et al., 2013; Gang et al., 2015; Kanemasa et al., 2017; Chen et al., 2016; Xu-Monette et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014; Candelaria et al., 2018; Pardal et al., 2018) was the most common clinical parameter that were used in a total of 24 studies, while 23 studies used LDH (lactate dehydrogenase) as one of the most common laboratory parameters (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Tomita et al., 2012; Lanic et al., 2012; Nols et al., 2014; Gang et al., 2015; Xu-Monette et al., 2016, 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Pardal et al., 2018) (Table 4).

One study reported a prognostic model assessed only by clinical parameters (Procházka et al., 2014), five based on laboratory parameters (Wilcox et al., 2011; Aoki et al., 2013; Batty et al., 2013; Ho et al., 2015; Ochi et al., 2017), a combination of clinical and laboratory parameters was used in 24 studies (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Conconi et al., 2000; Cox et al., 2008; Tomita et al., 2012; Huang et al., 2013; Gang et al., 2015; Kanemasa et al., 2017; Chen et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Matsumoto et al., 2018; Gao et al., 2018; Advani et al., 2010; Miura et al., 2017; Candelaria et al., 2018; Liu et al., 2018a; Pardal et al., 2018), clinical and immunohistochemical (IHC) parameters in 3 (Salles et al., 2011; Barrans et al., 2002; Xu-Monette et al., 2016), and a combination of clinical, imaging and/or molecular parameters in 4 (Lanic et al., 2012; Nols et al., 2014; Kong et al., 2016; Xu-Monette et al., 2016).

3.1. Findings

3.1.1. Clinical parameters

Only one study that exclusively evaluated clinical parameters (age, bulky disease, ECOG) was found. Although it provided internal validation, the model was not validated in an independent cohort (Procházka et al., 2014).

3.1.2. Laboratory parameters

A total of 7 studies proposed scores based on laboratory parameters only (Wilcox et al., 2011; Aoki et al., 2013; Batty et al., 2013; Jung et al., 2015; Ho et al., 2015; Ochi et al., 2017; Sun et al., 2018). Of these 4 analysed the influence of absolute lymphocyte count (ALC) in combination with absolute monocyte count (AMC) (Wilcox et al., 2011; Aoki et al., 2013; Batty et al., 2013; Ho et al., 2015). One study combined the lymphocyte-monocyte ratio (LMR), with the C-reactive protein (CRP) and albumin level (Sun et al., 2018), while another - combined - lactate dehydrogenase (LDH) with CRP and albumin level (Jung et al., 2015). One study analysed the influence of platelet count in combination with albumin level (Ochi et al., 2017). None of these studies had internal or external validation (Wilcox et al., 2011; Aoki et al., 2013; Batty et al., 2013; Jung et al., 2015; Ho et al., 2015; Ochi et al., 2017; Sun et al., 2018).

3.1.3. Combination of clinical and laboratory parameters

A total of 24 studies have combined clinical parameters and different laboratory parameters (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Conconi et al., 2000; Cox et al., 2008; Tomita et al., 2012; Huang et al., 2013; Gang et al., 2015; Kanemasa et al., 2017; Chen et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Matsumoto et al., 2018; Gao et al., 2018; Advani et al., 2010; Miura et al., 2017; Candelaria et al., 2018; Liu et al., 2018a; Pardal et al., 2018). Four studies have combined the same parameters (age, ECOG, extranodal – EN sites, stage, and LDH) that are included in the IPI (Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Advani et al., 2010). All of these studies, except one, have been validated in an external cohort of patients (Shipp et al., 1993; Ziepert et al., 2010; Hosoda et al., 2018; Sehn et al., 2007; Zhou et al., 2014; Advani et al., 2010; Procházka et al., 2014; Nicolaides et al., 1998; Biccler et al., 2018; Olszewski et al., 2015; Hong et al., 2011; Huang et al., 2012; Hong et al., 2017; Yang et al., 2017; Nakaya et al., 2016; Huang et al., 2015; Spiegel et al., 2017).

Beta-2-microglobulin (β2-M) was combined with clinical parameters in 7 studies (Conconi et al., 2000; Kanemasa et al., 2017; Chen et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Zhao et al., 2018; Candelaria et al., 2018), while the albumin level was used in 5 studies (Melchardt et al., 2015; Gang et al., 2015; Kobayashi et al., 2016; Miura et al., 2017; Liu et al., 2018a). Of the mentioned studies, two had internal (Kobayashi et al., 2016; Kang et al., 2017), and two had external validation (Montalbán et al., 2017; Miura et al., 2017; Liu et al., 2018a; Hong et al., 2017). Combination of clinical parameters and ALC, AMC and/or absolute neutrophil count (ANC) was used in 3 studies (Cox et al., 2008; Huang et al., 2013; Chen et al., 2016), of which only one was externally validated (Cox et al., 2008; Huang et al., 2013; Procházka et al., 2014; Bari et al., 2009). One study proposed a model using serum soluble interleukin-2 receptor (sIL-2R) levels in combination with the stage of disease and LDH. This model was validated on additional patients from the same institution few years later (Tomita et al., 2012, 2016). One study analysed lipid status in combination with

Table 1
Clinical parameters, laboratory parameters, immunohistochemical and molecular parameters per prognostic tool in general DLBCL population.

parameters	IPI (Shipp et al., 1993)	B2M-IPI (Conconi et al., 2000)	Barrans et al. (Barrans et al., 2002)	R-IPI (Sehn et al., 2007)	ALC/R-IPI (Cox et al., 2008)	Wilcox et al. (Wilcox et al., 2011)	Salles et al. (Salles et al., 2011)	sIL index (Tomita et al., 2012)	Lanic et al. (Lanic et al., 2012)	Modified 3-factor (Huang et al., 2013)	IMI (Aoki et al., 2013)	AMLPI (Batty et al., 2013)	NCCN-IPI (Zhou et al., 2014)	Nols et al. (Nols et al., 2014)	Melchardt et al. (Melchardt et al., 2015)	L-GPS (Jung et al., 2015)
CLINICAL																
Age	x	x		x									x		x	
ECOG	x	x		x						x			x		x	
EN sites	x	x		x									x		x	
Stage	x	x		x				x		x			x		x	
Bulky disease																
CCI																
BIOMARKERS																
LDH	x	x		x				x					x		x	x
ALC					x	x				x	x	x				
AMC						x					x	x				
LMR																
albumin															x	x
CRP																x
B2M		x														
PLT																
PLR																
Hb																
sIL-2R								x								
HDL-C, LDL-C																
IHC																
Bcl-2			x				x									
Myc																
Ki-67							x									
GC phenotype			x													
MOLECULAR																
GEP (ABC vs.GC)									x							
CD37																
RADIOLOGY																
Interim PET									x					x		
INDEX																
IPI			x				x									
aaIPI									x					x		
R-IPI					x											

parameters	DLBCL-PI (Gang et al., 2015)	ALC/AMC PS (Ho et al., 2015)	Kanemasa et al. (Kanemasa et al., 2017)	Kong et al. (Kong et al., 2016)	Chen et al. (Chen et al., 2016)	M-IPI-R (Xu-Monette et al., 2016)	IHC-IPI (Xu-Monette et al., 2016)	KPI (Kobayashi et al., 2016)	GELTAMO-IPI (Montalbán et al., 2017)	PA score (Ochi et al., 2017)	(Kang et al. (2017)	ICPS (Sun et al., 2018)	cNCCN-IPI (Antic et al., 2018)	Zhao et al. (Zhao et al., 2018)	Matsumoto et al. (Matsumoto et al., 2018)	Lipo-PI (Gao et al., 2018)
CLINICAL																
Age	x		x	x		x	x		x		x		x			x
ECOG	x		x		x	x	x	x	x		x		x			x
EN sites					x	x	x	x					x			x
Stage	x		x	x		x	x		x		x		x		x	x
Bulky disease																
CCI													x			
BIOMARKERS																
LDH	x					x	x	x	x		x		x			x

(*continued on next page*)

Table 1 (*continued*)

parameters	DLBCL-PI (Gang et al., 2015)	ALC/ AMC PS (Ho et al., 2015)	Kanemasa et al. (Kanemasa et al., 2017)	Kong et al. (Kong et al., 2016)	Chen et al. (Chen et al., 2016)	M-IPI-R (Xu-Monette et al., 2016)	IHC-IPI (Xu-Monette et al., 2016)	KPI (Kobayashi et al., 2016)	GELTAMO-IPI (Montalbán et al., 2017)	PA score (Ochi et al., 2017)	(Kang et al. (2017)	ICPS (Sun et al., 2018)	cNCCN-IPI (Antic et al., 2018)	Zhao et al. (Zhao et al., 2018)	Matsumoto et al. (Matsumoto et al., 2018)	Lipo-PI (Gao et al., 2018)
ALC		x			x											
AMC		x			x											
LMR												x				
albumin	x							x		x		x				
CRP												x				
B2M			x		x				x		x			x		
PLT										x						
PLR														x		
Hb															x	
sIL-2R																
HDL-C, LDL-C																x
IHC																
Bcl-2							x									
Myc							x									
Ki-67																
GC phenotype																
MOLECULAR																
GEP (ABC vs.GC)				x		x										
CD37						x	x									
RADIOLOGY																
Interim PET				x												
INDEX																
IPI																
aaIPI														x		
R-IPI																

ABC – Activated B cell; ALC – absolute lymphocytic count; AMC – absolute monocyte count; AMLPI – absolute monocyte and lymphocyte counts prognostic index; ALC/AMC PS- ALC/AMC prognostic score; aaIPI – age adjusted IPI; Bcl-2 – B cell lymphoma 2; B2M – β-2 microglobulin; CCI – Charlson Comorbidity Index; CRP – C reactive protein; cNCCN-IPI – comorbidity NCCN-IPI; DLBCL-PI - diffuse large B cell lymphoma prognostic index; ECOG – Eastern Cooperative Oncology Group; EN – Extranodal; GC – germinal centre; GEP – Gene expression profiling; Hb – haemoglobin; HDL-C – high-density lipoprotein cholesterol; IADL – Instrumental Activities of Daily Living; IACA – instrumental activities of daily living scale plus Age, Comorbidity, Albumin; ICPS – inflammation-based cumulative prognostic score system; IHC – immunohistochemistry; IHC-IPI – IPI plus immunohistochemistry; Interim PET – interim positron emission tomography; IPI – International Prognostic Index; IMI – immunological index; NCCN-IPI – National Comprehensive Cancer Network; M-IPI-R – molecularly adjusted IPI for R-CHOP; LDH – Lactate dehydrogenase; LDL-C – low-density lipoprotein cholesterol; L-GPS – LDH plus Glasgow prognostic score; LMR – lymphocyte to monocyte ratio; KPI – Kyoto Prognostic Index; Lipo-PI – lipoprotein prognostic index; PA score – Platelet-albumin score; PLT – platelets; PLR – platelet to lymphocyte ratio; R-IPI – revised-IPI; sIL-2R – soluble interleukin-2 receptor.

Table 2
Clinical parameters, laboratory parameters, immunohistochemical and molecular parameters per prognostic tool in elderly DLBCL population.

parameters	[aa] IPI* (Shipp et al., 1993)	E-IPI (Advani et al., 2010)	ABE4/ABE3-score (Procházka et al., 2014)	Alternative* NCCN-IPI for elderly (Melchardt et al., 2015)	ACA (Miura et al., 2017)	Saygin et al. (Saygin et al., 2017)	PA score* (Ochi et al., 2017)	cNCCN-IPI* (Antic et al., 2018)	Candelaria et al. (Candelaria et al., 2018)	IACA (Liu et al., 2018a)	Pardal et al. (Pardal et al., 2018)
CLINICAL											
Age		x	x	x	x			x			x
ECOG	x	x	x	x				x	x		
EN sites	x	x		x				x			
Stage	x	x		x				x			
Bulky disease			x						x		
CCI					x	x		x			
CIRS											x
IADL										x	
BIOMARKERS											
Hb									x		
LDH	x	x		x				x			
albumin					x		x				
B2M									x		
PLT							x				
INDEX											
IPI						x					
R-IPI											x
ACA										x	

[aa]IPI – age adjusted IPI; ABE – Age, bulk, ECOG; ACA – Age, Comorbidity, Albumin; B2M – β-2 microglobulin; CCI – Charlson Comorbidity Index; CIRS - Cumulative illness rating scale; cNCCN-IPI – comorbidity NCCN-IPI; ECOG – Eastern Cooperative Oncology Group; E-IPI – Elderly-IPI; EN – Extranodal; Hb –Haemoglobin; IADL – Instrumental Activities of Daily Living; IPI – International Prognostic Index; LDH – Lactate dehydrogenase; NCCN-IPI – National Comprehensive Cancer Network; R-IPI – Revised-IPI; PA score – Platelet-albumin.

NCCN-IPI (National Comprehensive Cancer Network-IPI) variables and performed internal validation (Gao et al., 2018).

Four studies incorporated comorbidities in prognostic models (Saygin et al., 2017; Antic et al., 2018; Miura et al., 2017; Pardal et al., 2018), with only one study that was validated by an independent cohort (Miura et al., 2017; Liu et al., 2018a). Anaemia was incorporated in prognostic models in two studies, that were neither internally or externally validated (Matsumoto et al., 2018; Candelaria et al., 2018).

3.1.4. Imaging parameters

Three studies incorporated interim Positron Emission Tomography (i-PET) in prognostic models (Lanic et al., 2012; Nols et al., 2014; Kong et al., 2016), with one study that was externally validated (Kong et al., 2016; Liu et al., 2018b). However, these studies were limited by the number of analysed patients (range 45–105).

3.1.5. Immunohistochemical (IHC) parameters

Three studies incorporated IHC parameters into IPI/ or IPI variables (Salles et al., 2011; Barrans et al., 2002; Xu-Monette et al., 2016). However, none of these studies have been externally or internally validated.

3.1.6. Molecular parameters

Three studies incorporated the results of gene expression profiling (GEP) analysis that determined the cell of origin, and combined it with clinical and/or imaging techniques (Lanic et al., 2012; Kong et al., 2016; Xu-Monette et al., 2016). One of these studies was externally validated (Kong et al., 2016; Liu et al., 2018b).

3.1.7. Models used in elderly patients

A total of 7 studies have proposed models that were built up - specifically on data from elderly patient populations (Saygin et al., 2017; Ochi et al., 2017; Advani et al., 2010; Procházka et al., 2014; Miura et al., 2017; Candelaria et al., 2018; Pardal et al., 2018). Of these 7 prognostic models for elderly patients, one had only internal validation (Procházka et al., 2014), while two were externally validated (Hosoda et al., 2018; Advani et al., 2010; Miura et al., 2017; Liu et al., 2018a).

Of 31 studies that were created for the general population, one study proposed refinement of point categorisation of NCCN-IPI variables for elderly patients, one showed better discriminatory power when only elderly populations were analysed, and two retained prognostic significance when tested on elderly patients (Shipp et al., 1993; Melchardt et al., 2015; Ochi et al., 2017; Antic et al., 2018). In total, 11 studies proposed scores that could be used in this specific group of patients.

3.1.8. Therapy

Regarding treatment of patients, 3 studies analysed patients who were treated without rituximab-based regiments (Shipp et al., 1993; Conconi et al., 2000; Barrans et al., 2002). Two studies included patients who received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or rituximab (R) plus CHOP-based regiments (Salles et al., 2011; Wilcox et al., 2011), while one study included patients that were treated with R-based regimens plus patients with primary DLBCL of the central nervous system (CNS) who received high doses methotrexate (MTX) (Antic et al., 2018). All other studies included patients who were treated with R-containing regiments, the majority of them with R-CHOP/R-CHOP-like therapy (Saygin et al., 2017; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Cox et al., 2008; Tomita et al., 2012; Lanic et al., 2012; Huang et al., 2013; Aoki et al., 2013; Batty et al., 2013; Nols et al., 2014; Jung et al., 2015; Gang et al., 2015; Ho et al., 2015; Kanemasa et al., 2017; Kong et al., 2016; Chen et al., 2016; Xu-Monette et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Ochi et al., 2017; Kang et al., 2017; Sun et al., 2018; Zhao et al., 2018; Matsumoto et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014; Miura et al., 2017; Candelaria et al., 2018; Liu et al., 2018a; Pardal et al., 2018).

3.1.9. Statistics

In all studies survival was calculated using Kaplan-Meier method and compared by the log-rank test. Uni- and/or multivariate analysis was assessed by a Cox proportional hazards regression in the majority of studies (Table 5).

Table 3
Summary of characteristics of each the included studies.

Index; author (publishing year)	No patients	Parameters (points)	risk Groups	% of paTients	OS (year)	OS (%)	Inclusion/ Exclusion criteria month and year of inclusion
IPI (Shipp et al., 1993)	2031	Age > 60 (1) ECOG > 1 (1) Stage III/IV (1) LDH > ULN (1) EN sites > 1 (1)	**L** (0–1) **LI** (2) **HI** (3) **H** (4–5)	35.0 27.0 22.0 16.0	5-	73.0 51.0 43.0 26.0	**Inclusion**: Aggressive B cell lymphoma; only patients who completed therapy by 1987 (1982-1987)
aa IPI	761	Stage III/IV (1) LDH > ULN (1) EN > 1 (1)	**L** (0) **LI** (1) **HI** (2) **H** (3)	18.0 31.0 35.0 16.0	5-	56.0 44.0 37.0 21.0	**Inclusion**: age > 60
aa IPI	1274	Stage III/IV (1) LDH > ULN (1) EN sites > 1 (1)	**L** (0) **LI** (1) **HI** (2) **H** (3)	22.0 32.0 32.0 14.0	5-	83.0 69.0 46.0 32.0	**Inclusion**: age≤60
β2M-IPI (Conconi et al., 2000)	71 (of 111)	Age > 60 (1) ECOG > 1 (1) Stage III/IV (1) LDH > ULN (1) EN > 1 (1) B2M > ULN (1)	**L** (0–1) **LI** (2) **HI** (3) **H** (4–6)	39.4 8.4 8.4 43.7	3-	~72.0 ~50.0 ~37.0 ~12.0	**Inclusion**: DLBCL; CHOP (1980-1995)
(Barrans et al., 2002)	155 (of 177)	IPI Bcl-2 GC expression	**L** (IPI L/I, Bcl-2-, GC+ **I** (IPI I without bcl-2 or GC expression **H** (IPI I/H, bcl-2+)	48.4 15.5 36.1	2-	68.0 50.0 20.0	**Inclusion**: available clinical data and histologic material; primary nodal de novo DLBCL; treatment (CHOP, Radiotherapy alone) **Exclusion**: PMBCL, Burkitt lymphoma, an underlying FL, anaplastic variants, PED (1985- 1997)
		IPI > 2 (1) Bcl-2 > 50% (1) lack of GC phenotype (1)	**score 0** **score 1** **score 2** **score 3**			84.0 75.0 40.0 7.0	
R-IPI (Sehn et al., 2007)	365	Age > 60 (1) ECOG > 1 (1) Stage III/IV (1) LDH > ULN (1) EN > 1 (1)	**Very good** (0) **Good** (1–2) **Poor** (3–5)	10.0 45.0 45.0	4-	94.0 79.0 55.0	**Inclusion**: Unselected DLBCL patients; R-CHOP **Exclusion**: HIV; secondary malignancy; underlying indolent lymphoma; major coincident illness (1981-January 2005)
ALC/R-IPI (Cox et al., 2008)	101	ALC < 0.84 × $10x^9$/l (1) R-IPI poor (1)	**L** (0) **I** (1) **H** (2)	49.0 35.0 17.0	1.8	92.0 81.0 56.0	**Inclusion**: DLBCL, PMBCL, associated/ developed from low grade lymphoma; age > 18; R-CHOP/R-CHOP-like therapy **Exclusion**: PCNSL; active HBV, HIV; prior chemo/steroid therapy in the previous 30 days (January 2003-March 2007)
E-IPI (Advani et al., 2010)	267	age ≤70 (1) LDH > 1xULN (1) ECOG 2-4 (1) Stage III/IV (1) EN sites > 1 (1)	**L** (0-1) **LI** (2) **HI** (3) **H** (4-5)	27.0 28.0 29.0 16.0	3-	86.0 74.0 58.0 36.0	**Inclusion**: DLBCL; R-CHOP; age≥60
ALC/AMC (Wilcox et al., 2011)	366	ALC≤1 × $10x^9$/l (1) AMC≥0.63 × $10x^9$/l (1)	**L** (0) **I** (1) **H** (2)	32.0 51.0 17.0	5-	~84.0 ~64.0 ~32.0	**Inclusion**: DLBCL; CHOP or R-CHOP **Exclusion**: HIV (1993-2007)
	256	Same as above		34.0 50.0 16.0	5-	~88.0 ~68.0 ~28.0	**Inclusion**: only R-CHOP treated cases
Model using biomarkers (Salles et al., 2011)*	284 (of 347)	IPI L vs. LI vs. HI vs. H Bcl-2 ≤ 75% vs. > 75% Ki-67 ≤ 75% vs. > 75%	**Group 1** **Group 2** **Group 3** **Group 4**	19.7 29.6 20.4 30.3	4-	94.0 81.0 62.0 45.0	**Inclusion**: treated with at least 6 cycles of CHOP/r CHOP-like with/without R; available data; available diagnostic paraffin samples (February 1998-August 2005)
SIL index (Tomita et al., 2012)	366	Stage ≥ III (1) sIL-2R ≥2500U/mL (1) LDH ≥ ULN (1)	**Standard** (0–1) **High** (2–3)	67.0 33.0	5-	89.0 62.0	**Inclusion**: DLBCL; R-CHOP in the beginning **Exclusion**: rR-CHOP from the beginning (min 20%); IVL, PMBCL, T/HRBCL; HIV (2003-2009)
aaIPI/i-PET/GEP (Lanic et al., 2012)	45 (of 57)	aaIPI 2-3 (1) i-PET slow metabolic response (1) GEP ABC(1)	**L** (0-1) **H** (2-3)	53.0 47.0	3-	~91.0 ~37.0	**Inclusion**: DLBCL; R-CHOP/R-CHOP l-like; available initial and i-PET; diagnostic samples for RNA from fresh/frozen tissues (October 2004-Janury 2009)
Modified 3-factor model (Huang et al., 2013)	274	ECOG > 1 (1) stage III/IV (1) ALC ≤1 × $10x^9$/l (1)	**score 0** **score 1** **score 2** **score 3**	32.0 34.0 25.0 9.0	3-	95.0 79.0 40.0 18.0	**Inclusion**: CD 20 + DLBCL; R-CHOP/R-CHOP-like **Exclusion**: PCNS involvement, HIV (January 2003-December 2009)

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Table 3 (*continued*)

Index; author (publishing year)	No patients	Parameters (points)	risk Groups	% of paTients	OS (year)	OS (%)	Inclusion/ Exclusion criteria month and year of inclusion
IMI (Aoki et al., 2013)	229	ALC $\leq 1.0 \times 10^9$/l (1) AMC $\geq 0.63 \times 10^9$/l (1)	**L** (0) **I** (1) **H** (2)	56.0 39.0 5.1	4-	83.8 59.3 18.8	**Inclusion**: DLBCL; R-CHOP **Exclusion**: IVBL, PEL, PMBCL, HIV, indolent (January 2004-January 2011)
AMLPI (Batty et al., 2013)	245	ALC $\leq 1 \times 10x^9$/l (1) AMC $\geq 0.61 \times 10x^9$/l (1)	**L** (0) **I** (1) **H** (2)	42.9 48.6 8.6	3-	~92.0 ~76.0 ~60.0	**Inclusion**: DLBCL; R-CHOP
NCCN-IPI (Zhou et al., 2014)	1650	Age < 40 (0); 40–60 (1); 60–75 (2); > 75 (3) LDH 1-3x ULN (1); > 3 × ULN (2) ECOG ≥ 2 (1) Stage III/IV (1) EN site ≥ 1 (1)	**L** (0-1) **LI** (2–3) **HI** (4–5) **H** (6-8)	19.0 42.0 31.0 8.0	5-	96.0 82.0 64.0 33.0	**Inclusion**: DLBCL; age > 18; R-CHOP; no more than one histologic subtype; HIV, HCV, HBV **Exclusion**: underlying lymphoma; secondary malignancy; major illness that preclude an attempt at curative therapy (June 2000-December 2011)
ABE 4 (Procházka et al., 2014)	379 (of 443)	Age ≥ 70 (1) bulky ≥ 7.5 cm (1) ECOG ≥ 1 (1)	**L** (0) **LI** (1) **HI** (2) **H** (3)	13.0 33.0 39.0 14.0	3-	94.0 77.0 63.0 35.0	**Inclusion**: DLBCL; age ≥ 60; R-CHOP **Exclusion**: CNS involvement (April 2002-May 2010)
ABE 3*	379 (of 443)	Age ≥ 70 (1); bulky ≥ 7.5cm (1); ECOG ≥ 1 (1)	**L*** **I** **H**	23.0 61.0 16.0	3-	92.0 67.0 36.0	
I-PET combined with IPI (Nols et al., 2014)*	73	aaIPI i-PET negative (DS 0-3)/positive (4-5); $\Delta SUV_{max} \leq 66\%$ vs. $\Delta SUV_{max} > 66\%$)	**group 1** **group 2** **group 3** **group 4**		3-	~90.0 ~75.6 ~50.0 0.0	**Inclusion**: anthracyclin-containing regimen + R (CHOP/CHOP-like, ACVBP); available initial and i-PET **Exclusion**: HIV, HBV, HCV (July 2003-November 2009)
modified NCCN-IPI + albumin (Melchardt et al., 2015)	499	Age < 40 (0); 40–60 (1); 60–75 (2); > 75 (3) LDH 1-3x ULN (1); > 3 × ULN (2) ECOG ≥ 2 (1) Stage III/IV (1) EN site ≥ 1 (1) Albumin < 35 g/l (2)	**L** (0–2) **LI** (3) **HI** (4–7) **H** (8–10)	24.0 19.0 49.0 8.0	5-	93.5 78.0 55.7 36.8	**Inclusion**: DLBCL; R-CHOP/R-CHOP like; **Exclusion**: HIV (2004-2013)
Alternative NCCN-IPI for elderly*	353?	Age > 60 (2) LDH > 1-3xULN (1); > 3xULN (2) ECOG ≥ 2 (1) Stage III/IV (1) EN sites > 1 (1)	**L** (2) **I** (3-5) **H** (≥ 6)	12.0 70.0 18.0	5-	89.0 56.5 32.3	**Inclusion**: age > 60
L-GPS (Jung et al., 2015)	213	hypoalbuminemia (1) CRP > 1 mg/dl (1) LDH > ULN (1)	**Score 0** (0) **Score 1** (1-2) **Score 2** (3)	35.2 51.2 13.6	5-	~87.0 ~61.0 ~20.0	**Inclusion**: CD20 + DLBCL; no prior chemo/radiotherapy; no infectious disease at the initiation of therapy; R-CHOP **Exclusion**: CNS involvement; HIV; NIID (RA) (2003-2011)
DLBCL-PI (Gang et al., 2015)	1803 (of 1990)	age > 70 (1) ECOG > 1 (1) LDH > ULN (1) Stage III/IV (1) albumin ≤ 40 g/l (1)	**L** (0-1) **LI** (2) **HI** (3) **H** (4-5)	33.1 26.1 23.1 17.7	5-	87.0 69.0 53.0 37.0	**Inclusion**: De novo DLBCL; R-CHOP/R-CHOP-like **Exclusion**: PCNSL; HIV; missing laboratory; no R-based therapy (2000-2010)
aaDLBCL-PI	1169 (of 1283)	ECOG > 1 (1) LDH > ULN (1) albumin ≤ 40 g/l (1) EN sites > 1	**L** (0) **LI** (1) **HI** (2) **H** (3-4)	27.2 30.8 25.3 16.7		92.0 84.0 74.0 47.0	**Inclusion**: aaDLBCL-PI ≤ 70 years
ALC/AMC PS (Ho et al., 2015)	148	ALC $\leq 1.162 \times 10x^9$/l (1) AMC > $0.555 \times 10x^9$/l (1)	**L** (0) **I** (1) **H** (2)	26.3 53.4 20.3	5-	94.4 71.2 41.0	**Exclusion**: PCNSL, testicular, breast lymphoma, paranasal involvement; patients who underwent not more than IV cy R-chemo (January 2001-December 2010)
A new risk model (b2M) (Kanemasa et al., 2017)	274	Age > 60 (1) ECOG > 1 (1) Stage III/IV (1) β2M ≥ 3.2 mg/l (1)	**L** (0) **LI** (1–2) **HI** (3) **H** (4)	9.5 59.1 18.2 13.1	3-	100.0 87.0 57.2 23.4	**Inclusion**: DLBCL; R-CHOP/R-CHOP-like **Exclusion**: HIV; CNS; transformed lymphoma from a prior indolent B cell lymphoma (September 2004-March 2015)
A new prognostic score for DLBCL (Kong et al., 2016)	105	Age > 60 (1) Stage III/IV (1) GEP ABC (1) Positive i-PET DS > 3 (1)	**L** (0-1) **LI** (2) **HI** (3) **H** (4)	61.9 21.9 8.6 7.6	3-	100.0 91.3 55.6 0.0	**Inclusion**: DLBCL; i-PET after II cy of therapy; R-CHOP **Exclusion**: PCNSL; children/adolescents (December 2009-October 2014)
the new prognostic model (Chen et al., 2016)	817	ANC > ULN (1); AMC > ULN (1) ECOG > 1 (1) EN site > 1 (1)	**L 1** (0) **L 2** (1) **I** (2)	13.0 24.0 21.0	5-	98.0 92.0 82.0	**Inclusion**: De novo DLBCL; R-CHOP/R-based/chemotherapy; 2 localized disease (radiotherapy); min II cy of chemotherapy

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Table 3 (*continued*)

Index; author (publishing year)	No patients	Parameters (points)	risk Groups	% of paTients	OS (year)	OS (%)	Inclusion/ Exclusion criteria month and year of inclusion
		β2 M 1–1.5 × ULN (1); 1.5–2 × ULN (2); > 2 × ULN (3)	**H 1** (3–5) **H 2** (6–7)	38.0 4.0		66.0 21.0	**Exclusion**: HIV; Secondary malignancy (October 2001- December 2011)
M-IPI-R (Xu-Monette et al., 2016)	1037	Age > 60 (1) ECOG > 1(1) Stage III/IV (1) LDH > ULN (1) EN sites > 1 (1) CD37 Negative (2) ABC subtype GEP (1)	**L** (0–1) **LI** (2–3) **I** (4) **HI** (5–6) **H** (7–8)	11.0 33.0 21.0 29.0 6.0	5-	~95.0 ~81.0 ~57.0 ~37.0 ~20.0	**Inclusion**: DLBCL; R-CHOP/CHOP; FFPE
IHC + IPI	1037	Age > 60 (1) ECOG > 1 (1) Stage III/IV (1) LDH > ULN (1) EN sites > 1 (1) CD37 Negative (3) Myc^{high} 70% (1) $Bcl\text{-}2^{high}$ 70% (1)	**L** (0–2) **LI** (3–4) **I** (5–6) **HI** (7–8) **H** (9–10)	19.0 28.0 33.0 16.0 4.0	5-	~91.0 ~78.0 ~50.0 ~24.0 ~8.0	
KPI (Kobayashi et al., 2016)	323	LDH > 1-3 (1); ≥3 (2) ECOG≥2 (1) Albumin < 35 g/l (1) EN≥1 (1)	**L** (0) **LI** (1-2) **HI** (3) **H** (4-5)	32.6 42.7 11.1 13.6	3-	96.4 84.7 63.8 33.3	**Inclusion**: R-CHOP/R-CHOP-like; **Exclusion**: HIV; other hematologic disease; transformed DLBCL; PCNSL; major coincident illness (January 2006-April 2014)
ACA index score (Miura et al., 2017)	555	Age > 75 (1) CCI≥3 (1) Albumin < 37 g/l (1)	**excellen**t (0) **good** (1) **moderate** (2) **poor** (3)	32.6 40.4 23.8 3.2	3-	86.0 72.0 51.0 0.0	**Inclusion**: age≥65 years; at least I cycle of R-CHOP **Exclusion**: disease involving CNS (January 2001 -December 2012)
Combined model (Saygin et al., 2017)	413	IPI 3-5 (1) CCI≥3 (1)	**L** (0) **I** (1) **H** (2)	35.5 55.9 8.6	5-	84.4 60.7 30.3	**Inclusion**: DLBCL; age≥60; received at least I cycle of treatment; R-CHOP/R-CHOP-like (2004-2014)
GELTAMO IPI (Montalbán et al., 2017)	1848	Age < 65 (0); 65–79 (1); ≥80 (2) ECOG 2 (1); 3–4 (2) Stage III/IV (1) LDH > ULN (1) β2M > ULN (1)	**L** (0) **LI** (1–3) **HI** (4) **H** (> 5)	11.0 58.0 17.0 14.0	5-	93.0 79.0 66.0 39.0	**Inclusion**: DLBCL all types; HBV, HCV, HIV; R-CHOP/or intensified; age > 18 **Exclusion**: CNS, testis; dose reduced therapy (January 1998 – July 2014)
PA score (Ochi et al., 2017)	391	Albumin < 35 g/l (1) Platelet count < 100 × $10x^9$/l (1)	**L** (0) **I** (1) **H** (2)	62.1 32.0 5.9	5-	81.5 48.6 20.2	**Inclusion**: DLBCL; R-based **Exclusion**: PMBCL, PEL, previous indolent lymphoma; HIV (January 2004-June 2014)
	291	Same as above	**L** (0) **I** (1) **H** (2)	58.8 34.7 6.5		77.6 47.9 19.0	**Inclusion**: age > 60
Modified prognostic model with b2M (Kang et al., 2017)	621	Age > 60 (1) LDH > ULN (1) ECOG > 2 (1) Stage III/IV (1) b2M > 2.5 mg/l (1)	**L** (0) **LI** (1) **HI** (2-3) **H** (4-5)	23.5 24.6 37.5 14.3	5-	95.2 86.4 69.2 47.8	**Inclusion**: de novo DLBCL; R-CHOP; age > 20; life expectancy > 6 month **Exclusion**: CNS (March 2004-June 2012)
ICPS (Sun et al., 2018)	564	CRP > 8.6 mg/l (1) Albumin < 41.5 g/l (1) LMR≤2.7 (1)	**ICPS 0** **ICPS 1** **ICPS 2** **ICPS 3**	35.8 25.5 17.6 21.1	3-	95.6 88.2 76.0 62.2	**Inclusion**: DLBCL; R-CHOP **Exclusion**: Therapy other than R-CHOP; dose reduced > 20%; not completed R-CHOP; CNS, HIV; acute infection/chronic inflammation (November 2006-December 2013)
cNCCN-IPI (Antic et al., 2018)	958 (of 962)	CCI≥2 (3) + NCCN-IPI variables/scoring	**L** (0) **LI** (1-2) **HI** (3-5) **H** (6-11)	3.4 34.3 49.4 12.5	5-	100.0 79.0 50.0 14.0	**Inclusion**: DLBCL; no history of previous lymphoma; min I cy of therapy; R-based therapy/high dose MTX for CNS patients (January 2000-December 2015)
	426	Same as above	**LI** (1-2) **HI** (3-5) **H** (≥6)	16.4 58.5 24.4	5-	59.0 51.0 15.0	age≥60
(Candelaria et al., 2018)	141	ECOG: 1 (1); 2 (2); 3 (3) b2M: N (1); > N (2) Bulky disease: No (1); Yes (2) Hb: > 100 g/l (1); < 100 g/l (2)	**L**≤5 **I** = 6 **H** > 6		5-	80.1 55.5 29.4	**Inclusion**: DLBCL; age≥65; R-CHOP/R-CHOP like; HIV (January 2011-June 2015)
Novel prognostic scoring system* (Zhao et al., 2018)	309	PLR < 170 IPI/or aaIPI b2M	**L** **I** **H**		5-	86.4 54.1 21.1	**Inclusion**: DLBCL; R-CHOP **Exclusion**: history of malignancy; immunosuppression or previous treatment (March 2009-February 2015)
IACA index (Liu et al., 2018a)	99	IADL 6-7 (1); ACA good (1)			2-		

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Table 3 (*continued*)

Index; author (publishing year)	No patients	Parameters (points)	risk Groups	% of paTients	OS (year)	OS (%)	Inclusion/ Exclusion criteria month and year of inclusion
		IADL ≤ 5 (2); ACA moderate to poor (2)	**L** (0)	39.4		96.0	**Inclusion**: DLBCL; age ≥ 65; R-CHOP/R-CHOP like
			I (1-2)	44.4		70.1	
			H (3-4)	16.2		24.1	(January 2003-December 2016)
(Pardal et al., 2018)	108 (of 251)	Age > 85 (1) R-IPI 3-5 (1) CIRS > 5 (1)	**0-1 risk factors**		3-	58.0	**Inclusion**: age ≥ 80; DLBCL de novo/ transformed/FL grade 3b; R-CHOP/rR-CHOP
			2-3 risk factors			25.0	(January 2002-December 2014)
(Matsumoto et al., 2018)	185	Stage ≥ 3 (1) Anaemia ≥ Gr 2 (1)	**Score 0**	42.7	3-	94.6	**Inclusion**: R-CHOP
			Score 1	43.8		82.0	**Exclusion**: transfer to another hospital; cancer; early death; lack of information; other therapy
			Score 2	13.5		61.4	(2004-2014)
Lipo-PI (Gao et al., 2018)	367	Normal lipid level (0) Low HDL-C/or low LDL-C (1) Low HDL-C < 1.03 mmol/l and low LDL-C < 2.60 mmol/l (2) + NCCN-IPI variables/scoring	**L** (0-2)		5-	96.9	**Inclusion**: no liver diseases/or previous malignancies; complete data; R-CHOP/R-CHOP-like; no treatment with drugs known to affect lipid metabolism (statins/ fibrates) **Exclusion**: HIV (January 2006-December 2016)
			LI (3-4)			79.6	
			HI (5-6)			45.0	
			H (7-10)			22.5	

*look in original article for calculation; aaDLBCL PI – age adjusted DLBCL PI; aaIPI – age adjusted IPI; ABC – Activated B cell; ABE – Age, bulk, ECOG; ACA – Age, Comorbidity, Albumin; ACVBP – doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; ALC – Absolute lymphocytic count; AMC – Absolute monocyte count; AMPLI – Absolute monocyte and lymphocyte counts prognostic index; PS – prognostic score; ANC – Absolute neutrophil count; B-2M – β-2 microglobulin; Bcl-2 – B cell lymphoma 2; CCI – Charlson Comorbidity Index; cNCCN-IPI – Comorbidity NCCN-IPI; CNS – Central nervous system; CIRS – Cumulative illness rating scale; CHOP – Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; CRP – C reactive protein; ΔSUVmax – Maximum standardized uptake value; DLBCL – Diffuse large B cell lymphoma; DLBCL PI – DLBCL prognostic index; DS – Deauville score; ECOG – Eastern Cooperative Oncology Group; EN – Extranodal; E-IPI – Elderly IPI; FL – Follicular lymphoma; FFPE – Formalin-fixed, paraffin embedded; GC – Germinal centre; GEP – Gene expression profiling; GI – Gastrointestinal; Gr – Grade; H – High; HBV – Hepatitis B virus; HCV – Hepatitis C virus; HDL-C – High-density lipoprotein cholesterol; HI – High intermediate; HIV – Human immunodeficiency virus; I – Intermediate; IADL – Instrumental Activities of Daily living; ICPS – Inflammation-based cumulative prognostic score system; IHC – Immunohistochemistry; IHC + IPI – IPI plus immunohistochemistry; i-PET – Interim-positron emission tomography; IPI – International Prognostic Index; IPI L – IPI low; IPI I – IPI intermediate (low intermediate and high intermediate); IPI LI – IPI low intermediate; IPI H – IPI high; IPI HI – IPI high intermediate; IMI – Immunological index; IVBL – Intravascular B lymphoma; KPI – Kyoto Prognostic Index; L – Low; LDH – Lactate dehydrogenase; ULN – Upper limit normal; LDL-C – Low-density lipoprotein cholesterol; L-GPS – LDH plus Glasgow prognostic score; LMR – lymphocyte to monocyte ratio; Lipo-PI – Lipoprotein prognostic index; LI – Low intermediate; M-IPI-R – Molecularly adjusted IPI for R-CHOP; MTX – Methotrexate; NCCN-IPI – National Comprehensive Cancer Network; NIID – Non-infectious inflammatory disease; PA score – Platelet-albumin score; PCNSL – Primary central nervous system lymphoma; PED – Primary extranodal disease; PEL – Primary effusion lymphoma; PLR – Platelet to lymphocyte ratio; PMBCL – Primary mediastinal B cell lymphoma; R – Rituximab; RA – Rheumatoid arthritis; R-CHOP – Rituximab-CHOP; R-IPI – Revised-IPI; RNA – Ribonucleic acid; rR-CHOP – Reduced R-CHOP; sIL-2R – Soluble interleukin-2 receptor; T/HRBCL – T-cell/histiocyte-rich B-cell lymphoma.

Twenty-four studies reported no direct differences to other previously proposed models (Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Wilcox et al., 2011; Tomita et al., 2012; Lanic et al., 2012; Aoki et al., 2013; Batty et al., 2013; Nols et al., 2014; Jung et al., 2015; Ho et al., 2015; Kong et al., 2016; Xu-Monette et al., 2016; Ochi et al., 2017; Sun et al., 2018; Zhao et al., 2018; Matsumoto et al., 2018; Miura et al., 2017; Candelaria et al., 2018; Liu et al., 2018a; Pardal et al., 2018).

Generally, the majority of studies that evaluated combination of clinical and/or laboratory parameters compared proposed scores to previously reported models such as IPI, aaIPI, R-IPI, and NCCN-IPI (Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Huang et al., 2013; Gang et al., 2015; Kanemasa et al., 2017; Chen et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014). Performance of indices was evaluated by a measure of global fit (Akaike's information criteria, AIC), by a measure of discrimination (concordance probability estimate, CPE), and/or by the area under the receiver operating characteristic curve (ROC) for survival outcomes (c-index) in 13 studies. One study applied Hosmer-Lemeshow goodness-of-fit to the reclassified categories (Montalbán et al., 2017).

ABC – Activated B cell; ALC – Absolute lymphocytic count; AMC – Absolute monocyte count; ANC – Absolute neutrophil count; B-2M – β-2 microglobulin; Bcl-2 – B cell lymphoma 2; CCI – Charlson Comorbidity Index; CIRS – Cumulative illness rating scale; CRP – C reactive protein; ECOG – Eastern Cooperative Oncology Group; EN – extranodal; GC – Germinal centre; GEP – gene expression profiling; Hb – Haemoglobin; IADL – Instrumental Activities of Daily living; Interim PET – Positron emission tomography; IHC – Immunohistochemistry; LDH – Lactate dehydrogenase; LMR – lymphocyte to monocyte ratio; PLT – platelets; sIL-2R – Soluble interleukin-2 receptor

4. Discussion

The IPI is the most commonly used prognostic model for patients with DLBCL (Shipp et al., 1993; Sehn et al., 2007). Due to its' easily accessible parameters and its predictive capacity, the IPI has gained universal acceptance (Sehn et al., 2007). However, the main limitations of the IPI are that the study population comprised histologically varying, aggressive lymphomas, treated before the introduction of rituximab. Several studies have pointed to a decreased prognostic value of the IPI in the rituximab era, as well as the necessity for a new prognostic index in DLBCL, capturing our growing knowledge of disease pathobiology (Zhou et al., 2014; Sehn, 2012). The prognostic significance of the parameters included in the IPI has been re-evaluated in rituximab-treated DLBCL patients in several studies (Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Advani et al., 2010). Of special interest is NCCN-IPI, that has a refined categorisation for age, and LDH (Zhou et al., 2014). Furthermore, this score derives from an unselected population of DLBCL patients treated with rituximab based combinations, and both internally and externally validated (Hosoda et al., 2018; Zhou et al., 2014; Melchardt et al., 2015; Montalbán et al., 2017; Biccler et al., 2018; Hong et al., 2017; Yang et al., 2017; Nakaya et al., 2016; Huang et al., 2015; Spiegel et al., 2017).

In order to further improve prognostication of patients with DLBCL a number of laboratory parameters were combined with the IPI

Table 4
Summary of statistical methods, median overall survival, follow up and validation process for each study.

Index; Author (publishing year)	Statistics	Median age years (range)	Median follow up - months (range)	Internal/ External validation
IPI, aa-IPI; Shipp et al., (1993)	No direct comparison to other proposed prognostic models		36 all; 54 censored	Yes/Yes (Ziepert et al., 2010; Hosoda et al., 2018; Nicolaides et al., 1998; Biccler et al., 2018; Olszewski et al., 2015)
B2M-IPI; (Conconi et al., 2000)	Comparison of sensitivity IPI vs. b2M-IPI (from 45 to 73%)	64 (25-89)	72 on 111 cases	No/No
(Barrans et al., 2002)	No direct comparison to other proposed prognostic models	66 (11-90)	26 (0-180) on 177 cases	No/No
R-IPI; Sechn et al. (2007)	No direct comparison to other proposed prognostic models	61 (16-90)	33 (7-64) censored	No/Yes (Hosoda et al., 2018; Biccler et al., 2018; Olszewski et al., 2015; Hong et al., 2011; Huang et al., 2012)
ALC/R-IPI ; (Cox et al., 2008)	No direct comparison to other proposed prognostic models		22 (2-52)	No/Yes (Huang et al., 2013; Procházka et al., 2014; Bari et al., 2009)
E-IPI; (Advani et al., 2010)	IPI (AIC:1155; CPE: 0.63; 95% CI, 0.58, 0.67); aaIPI (AIC:1163; CPE: 0.62; 95% CI, 0.57, 0.66); R-IPI (AIC: 1168; CPE: 0.59; 95% CI, 0.55, 0.64); E-IPI (AIC: 1147; CPE: 0.66; 95% CI, 0.61; 0.70)	69 (60-92)		No/Yes (Hosoda et al., 2018; Procházka et al., 2014)
ALC/AMC; (Wilcox et al., 2011)	No direct comparison to other proposed prognostic models	64 (20-92)	50 (< 1-146) all/66 censored cases	No/No
model usinG biomarkers (Salles et al., 2011)	Proposed model vs. IPI (BIC: 1145 vs. 1153; c-index: 0.69 vs. 0.67)	Age > 60 67% pts	52.8	No/No
SIL index; (Tomita et al., 2012)	No direct comparison to other proposed prognostic models (% of OS)	64 (18-80)	43 (3-95) censored cases	Yes/No (Tomita et al., 2016)
aaIPI/interim PET/GEP; (Lanic et al., 2012)	No direct comparison to other proposed prognostic models	65 (22-87)	28 (7 – 73)	No/No
Modified three-factor model; (Huang et al., 2013)	IPI (AIC:798.715); R-IPI (AIC: 791.263); ALC/R-IPI (AIC: 780.935); Modified 3-factor model (AIC: 771.102)	70 (16-88)	25.2	No/No
IMI; (Aoki et al., 2013)	No direct comparison to other proposed prognostic models	69 (23-90)	43.5 (1-100)	No/No
AMLPI; (Batty et al., 2013)	No direct comparison to other proposed prognostic models	60 (19-92)	22 (0.03-42)	No/No
NCCN-IPI; (Zhou et al., 2014)	IPI (AIC: 4627; CPE: 0.74; 95% CI, 0.71, 0.78); NCCN-IPI (AIC: 4566; CPE: 0.8; 95% CI, 0.77, 0.83)	57	37	Yes/Yes (Hosoda et al., 2018; Melchardt et al., 2015; Montalbán et al., 2017; Biccler et al., 2018; Hong et al., 2017; Yang et al., 2017; Nakaya et al., 2016; Huang et al., 2015; Spiegel et al., 2017) 1650 training/1138 validation
ABE 4; (Procházka et al., 2014)	ABE4 (AIC: 1304; measure of concordance: 0.686; 0.637, 0.735) IPI (AIC: 1336; measure of concordance: 0.635; 0.584,0.686) aaIPI (AIC 1325; measure of concordance: 0.650; 0.599, 0.701) E-IPI (AIC: 1292; measure of concordance: 0.665; 0.614, 0.716)	70 (60-88)	60.7 censored (443 cases)	Yes/No 379 training/162 patients in validation cohort a year after collecting data
ABE 3* (Proscházaka et al., 2014)	ABE 3 (AIC:1299; measure of concordance: 0.676; 0.631, 0.721) R-IPI (AIC: 1340; measure of concordance: 0.605; 0.558, 0.652) ALC/R-IPI (AIC: 1337; measure of concordance: 0.619; 0.570, 0.668)			
(Nols et al., 2014)	No direct comparison to other models	60 (18-85)	28.8 (3.6-85.2)	No/No
modified NCCN-IPI + albumin; (Melchardt et al., 2015)	NCCN-IPI + albumin vs. NCCN-IPI (CPE: 0.783 vs. 0.753) Elderly patients: IPI vs. NCCN-IPI vs. modified NCCN-IPI (CPE: 0.637 vs. 0.674 vs. 0.723)	65.3 (20-92)	51 censored cases	No/No
L-GPS; (Jung et al., 2015)	No direct comparison to other proposed prognostic models	58 (17-85)	32.8 (< 1 to 81)	No/No
DLBCL-PI; (Gang et al., 2015)	DLBCL PI vs. IPI (C-index: 0.77 vs. 0.73, $p < 0.0001$)	65 (16-95)	52.8 censored cases	No/No
[aa]DLBCL-PI	[aa]DLBCL PI vs. aaIPI (C-index: 0.79 vs. 0.76, $p = 0.007$)	60 (16-70)		
ALC/AMC PS; (Ho et al., 2015)	No direct comparison to other proposed prognostic models	61 (16-88)	53.28 (0.7-146.6)	No/No
A new risk model (b2M); (Kanemasa et al., 2017)	New risk model vs. NCCN-IPI (AIC: 662.5 vs. 678.1; CPE: 0.781 vs. 0.760)	69 (27-97)	37 censored cases	No/No
A new prognostic score; (Kong et al., 2016)	No direct comparison to other proposed prognostic models	56 (19-82)	32 (9-59)	No/Yes (Liu et al., 2018b)
(Chen et al., 2016)	New model vs. IPI (C index: 0.75, 95% CI, 0.67–0.81; vs. C-index: 0.71, 95% CI, 0.63–0.78)	58 (18-91)	60.4 (1–143)	No/No
M-IPI-R / IHC + IPI; (Xu-Monette et al., 2016)	No direct comparison to other proposed prognostic models (only comparison of OS in %)			No/No
KPI; (Kobayashi et al., 2016)	R-IPI vs. NCCN-IPI vs. KPI (C-index: 0.642 vs. 0.736 vs. 0.740); KPI vs. R-IPI vs. NCCN-IPI (RBSR: 30.5% vs. 13.5% vs. 25.1%)	70 (23-94)	2.6	Yes/No 323 training/142 validation

(*continued on next page*)

Table 4 (*continued*)

Index; Author (publishing year)	Statistics	Median age years (range)	Median follow up - months (range)	Internal/ External validation
ACA index score; (Miura et al., 2017)	No direct comparison to other proposed prognostic models	74 (65-96)		Yes/Yes (Liu et al., 2018a) 555 training/281 validation
Combined model; (Saygin et al., 2017)	No direct comparison to other proposed prognostic models (given OS in % to compare with IPI)	69 (60-100)	37.5 (1-260)	No/No
GELTAMO IPI (Montalbán et al., 2017)	Hosmer-Lemeshow goodness-of-fit GELTAMO-IPI vs NCCN-IPI (χ^2 = 9.54; p = 0.299; vs. χ^2 = 16.40; p = 0.037)	60	57	Yes/Yes (Hong et al., 2017) 1230 training/618 validation
PA score; (Ochi et al., 2017)	No direct comparison to other proposed prognostic models	70(21-104)	52.4 (1-143) censored	No/No
Modified prognostic model with b2MG; (Kang et al., 2017)	IPI (C-index: 0.705, 95% CI, 0.659–0.751) vs. NCCN-IPI (C-index: 0.710, 95% CI, 0.664– 0.757) vs. modified prognostic model (C-index: 0.739; 95% CI, 0.691–0.786)	57 (16-85)		Yes/No 621 training/434 validation
ICPS; (Sun et al., 2018)	No direct comparison to other proposed prognostic models	53 (18-89)	31.5	No/No
cNCCN-IPI; (Antic et al., 2018)	cNCCN-IPI vs. NCCN-IPI (AUC: -0.013, 95% CI, -0.024; -0.001, p < 0.05) cNCCN-IPI vs. IPI (AUC: -0.021, 95% CI, -0.038;-0.005, p < 0.05)	58 (18-89)	36 (1-180)	No/No
elderly patients (Antic et al., 2018)	cNCCN-IPI vs. IPI (AUC: -0.051, 95% CI; -0.083, 0.0193, p < 0.05) cNCCN-IPI vs. NCCN-IPI (AUC: -0.036, 95% CI; -0.058, -0.013, p < 0.05)			
(Candelaria et al., 2018)	No direct comparison to other proposed prognostic models	74 ± 6.6		No/No
(Zhao et al., 2018)	No direct comparison to other proposed prognostic models	58 (16-90)	47 (1-83)	No/No
IACA index ; (Liu et al., 2018a)	No direct comparison to other proposed prognostic models	(65-92)		No/No
(Pardal et al., 2018)	No direct comparison to other proposed prognostic models	82 (80-92)	44 (12-142)	No/No
(Matsumoto et al., 2018)	No direct comparison to other proposed prognostic models	66 (21-83)	55.3 (4.8-117)	No/No
Lipo-PI;(Gao et al., 2018)	Lipo-PI vs. NCCN-IPI (AUC: 0.835 vs 0.766; C-index: 0.802 vs 0.751)	58 (14-88)	(7-135)	Yes/No 367 training/183 validation

^{aaDLBCL}-PI – age adjusted diffuse large B cell lymphoma prognostic index; aa IPI – age adjusted IPI; ABE – Age, bulk, ECOG; ACA – Age, Comorbidity, Albumin; AIC – Akaike's information criteria; ALC – absolute lymphocytic count; AMC – absolute monocyte count; AMPLI – Absolute monocyte and lymphocyte counts prognostic index; AUC – area under the curve; B2M – β-2 microglobulin; BIC – Bayesian information criterion; CI – Confidence interval; cNCCN-IPI – comorbidity NCCN-IPI; CPE – concordance probability estimate; E-IPI – Elderly-IPI; GEP – Gene expression profiling; IACA – IADL (Instrumental Activities of Daily Living) and ACA; ICPS – Inflammation-based cumulative prognostic score system; IHC + IPI – IPI plus immunohistochemistry; IMI – immunological index; Interim PET – interim positron emission tomography; IPI – International Prognostic Index; KPI – Kyoto Prognostic Index; L-GPS – LDH plus Glasgow prognostic score DLBCL-PI; Lipo-PI – Lipoprotein prognostic index; M-IPI-R – Molecularly adjusted IPI for R-CHOP; NCCN-IPI – National Comprehensive Cancer Network; RBSR – relative Brier score reduction; R-IPI – Revised-IPI; sIL – Soluble interleukin; OS – Overall survival; PA score – Platelet-albumin; PS – prognostic score.

Table 5
Summary of number of studies per each parameter that were used in prognostic model, with given references.

Parameters	No of studies	References
CLINICAL		
Age	22	(Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Gang et al., 2015; Kong et al., 2016; Xu-Monette et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014; Miura et al., 2017; Liu et al., 2018a; Pardal et al., 2018)
ECOG	24	(Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Huang et al., 2013; Gang et al., 2015; Kanemasa et al., 2017; Chen et al., 2016; Xu-Monette et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Procházka et al., 2014; Candelaria et al., 2018; Pardal et al., 2018)
EN involvement	18	(Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Nols et al., 2014; Gang et al., 2015; Chen et al., 2016; Xu-Monette et al., 2016; Kobayashi et al., 2016; Antic et al., 2018; Gao et al., 2018; Advani et al., 2010; Pardal et al., 2018)
Ann Arbor stage of disease	24	(Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Tomita et al., 2012; Lanic et al., 2012; Nols et al., 2014; Gang et al., 2015; Kanemasa et al., 2017; Kong et al., 2016; Xu-Monette et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Matsumoto et al., 2018; Gao et al., 2018; Advani et al., 2010; Pardal et al., 2018)
Bulky disease	2	(Procházka et al., 2014; Candelaria et al., 2018)
Comorbidities (CCI/CIRS)	4	(Saygin et al., 2017; Miura et al., 2017; Liu et al., 2018a)/ (Pardal et al., 2018)
IADL	1	(Liu et al., 2018a)
BIOMARKERS		
LDH	23	(Saygin et al., 2017; Shipp et al., 1993; Sehn et al., 2007; Zhou et al., 2014; Melchardt et al., 2015; Salles et al., 2011; Conconi et al., 2000; Barrans et al., 2002; Cox et al., 2008; Tomita et al., 2012; Lanic et al., 2012; Nols et al., 2014; Jung et al., 2015; Gang et al., 2015; Xu-Monette et al., 2016; Kobayashi et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Antic et al., 2018; Zhao et al., 2018; Gao et al., 2018; Advani et al., 2010; Pardal et al., 2018)
ALC	5	(Cox et al., 2008; Wilcox et al., 2011; Huang et al., 2013; Aoki et al., 2013; Batty et al., 2013)
AMC	4	(Wilcox et al., 2011; Aoki et al., 2013; Batty et al., 2013; Chen et al., 2016)
LMR	1	(Sun et al., 2018)
ANC	1	(Chen et al., 2016)
albumin	6	(Melchardt et al., 2015; Jung et al., 2015; Gang et al., 2015; Kobayashi et al., 2016; Ochi et al., 2017; Miura et al., 2017; Liu et al., 2018a)
CRP	2	(Jung et al., 2015; Sun et al., 2018)
B2M	7	(Conconi et al., 2000; Kanemasa et al., 2017; Chen et al., 2016; Montalbán et al., 2017; Kang et al., 2017; Zhao et al., 2018; Candelaria et al., 2018)
PLT	2	(Ochi et al., 2017; Zhao et al., 2018)
Hb	2	(Matsumoto et al., 2018; Candelaria et al., 2018)
sIL-2R	1	(Tomita et al., 2012)
Lipid status	1	(Gao et al., 2018)
IHC		
Bcl-2	3	(Salles et al., 2011; Barrans et al., 2002; Xu-Monette et al., 2016)
Ki-67	1	(Salles et al., 2011)
Myc	1	(Xu-Monette et al., 2016)
CD37 expression	1	(Xu-Monette et al., 2016)
GC phenotype	1	(Barrans et al., 2002)
MOLECULAR		
GEP (ABC vs. GC)	3	(Lanic et al., 2012; Kong et al., 2016; Xu-Monette et al., 2016)
IMAGING		
Interim PET	3	(Lanic et al., 2012; Nols et al., 2014; Kong et al., 2016)

variables. The prognostic role of decreased albumin level was used as a sign of unfavourable biology, inability to tolerate chemotherapy, due to comorbid conditions, high risk EN sites and poor nutritional status, was confirmed in the large Danish population (Gang et al., 2015). By combining low serum albumin with clinical parameters, it is possible to overcome classical risk factors such as old age, increased LDH and advanced stage of the disease (Melchardt et al., 2015; Gang et al., 2015; Ochi et al., 2017). Another biomarker - β2 M has been combined with the IPI variables in non-rituximab treated patients (Conconi et al., 2000). In the rituximab era, β2 M incorporated in a new risk models, lead to superior prognostic power compared to NCCN-IPI (Kanemasa et al., 2017; Montalbán et al., 2017) or the IPI (Kang et al., 2017; Zhao et al., 2018). This parameter was also combined with other clinical parameters (Kanemasa et al., 2017; Chen et al., 2016) and/or laboratory parameters (Chen et al., 2016; Candelaria et al., 2018), as well as IHC (Salles et al., 2011; Barrans et al., 2002). However, limitations of these studies include: number of analysed patients, retrospective nature, selection bias due to missing data in some patients, no data of potential influence of renal failure on serum β2 M level and lack of external validation.

Based on the increasing evidence that the presence of a systemic inflammatory response is related to the outcome of lymphoma patients, several prognostic scores incorporated CRP concentration, or platelet counts as inflammatory parameters (Jung et al., 2015; Sun et al., 2018; Zhao et al., 2018). However, due to the retrospective nature of these studies, it is not easy to differentiate the causes of elevated CRP in complicating infectious disease and genuine tumour derived inflammation (Sun et al., 2018; Zhao et al., 2018). The role of lipid status (Gao et al., 2018) and anaemia has been modestly investigated, mainly in the retrospective, not-validated studies with limited number of patients (Matsumoto et al., 2018).

By using GEP, it is demonstrated that the length of survival of NHL patients is associated, to a large degree, with the molecular features of non-malignant immune cells present in the tumour at the time of diagnosis (Rosenwald et al., 2002; Dave et al., 2004; Lenz et al., 2008; Alizadeh et al., 2000; Gutierrez-Garcia et al., 2011). ALC and AMC derived from pre-treatment cell blood counts were tested as potential surrogate biomarkers of the host's adaptive immunity and immune microenvironment. ALC was used in prognostic models based on its prognostic relevance in NHL, while AMC was used because myeloid-lineage cells promote tumorigenesis by contributing to the suppression of their host's antitumor immunity and by stimulating tumour

angiogenesis (Cox et al., 2008; Wilcox et al., 2011; Huang et al., 2013; Aoki et al., 2013; Chen et al., 2016; Porrata et al., 2010). However, these studies are limited by the number of patients, short follow-up, and the lack of consensus regarding relevant ALC/or AMC cut-off points (Cox et al., 2008).

An early attempt to improve prognostic significance of the IPI by addition of IHC variables was made more than 15 years ago (Barrans et al., 2002). A new insight in DLBCL pathobiology was made by introduction of GEP, but its incorporation into daily practice remains a challenge due to high costs and the necessity for technical support (Wilcox et al., 2011; Rosenwald et al., 2002; Lenz et al., 2008). Although, many attempts were made to transfer molecular classification into an IHC score, stratification based on IHC algorithms cannot accurately predict GEP subtypes (Salles et al., 2011; Gutierrez-Garcia et al., 2011). Therefore, expression of individual biomarkers such as Bcl2, Ki-67, Myc, or CD37 were combined with clinical parameters in three studies (Salles et al., 2011; Barrans et al., 2002; Xu-Monette et al., 2016). However, the inability of these biomarkers to further stratify outcome of high-risk IPI patients may reflect the superiority and robustness of patient characteristics over the biological characteristics of tumour cells (Salles et al., 2011; Schmidt-Hansen et al., 2017; Scott et al., 2014).

Functional imaging of tumour with [18 F]-fluorodeoxyglycose PET (FDG-PET) at diagnosis and after a few cycles of chemotherapy (i-PET) could be helpful in optimizing initial DLBCL staging and assessment treatment response (Lanic et al., 2012). Several studies proposed models based on clinical parameters, i-PET and/or molecular features of the lymphoma determined by GEP (Lanic et al., 2012; Nols et al., 2014; Kong et al., 2016; Xu-Monette et al., 2016). The interpretation of i-PET is not always reproducible, and the rate of false-positive interim scans is not insignificant (Wilcox et al., 2011; Lanic et al., 2012; Itti et al., 2009; Barrington and Mikhaeel, 2016). The idea of combining clinical parameters, biomarkers, i-PET (that shows changes of tumour metabolic activity and reflects the objective interim treatment response during treatment), with/without molecular parameters (that reflect the initial state of disease and genetic heterogeneity) is quite appealing and inspired by the successful PET-adapted treatment guidance successfully implemented in the treatment of Hodgkin lymphoma. However, these studies are limited due to their retrospective nature, and small number of patients, which makes application of these proposed models questionable (Lanic et al., 2012; Nols et al., 2014; Kong et al., 2016).

In the elderly population the incidence of DLBCL rises with close to 50% of patients being older than 70, and the older age is associated with the poorer outcomes (Saygin et al., 2017). The IPI had split the population into 2 age groups: ≤ 60 and > 60. This is based on availability of intensive treatment which is restricted to younger patients (Shipp et al., 1993). The introduction of rituximab has resulted in similar dose intensity of therapies in both younger and older patients (Pfreundschuh et al., 2011, 2006; Pfreundschuh et al., 2008). However, being > 70 years old has since been recognised as an adverse factor, largely due to therapy-related toxicity and inability to complete planned therapy (Pfreundschuh et al., 2008). This age limit was used in several prognostic scores that analysed elderly patients (Advani et al., 2010; Procházka et al., 2014). NCCN-IPI excluded elderly patients from low risk group due to the higher risks that age brings. An alternative NCCN-IPI for the elderly was proposed, because the fit patients are not adequately recognised by the NCCN-IPI, but could be eligible for an intensified regime, in the absence of other risk factors (Melchardt et al., 2015). Furthermore, compared to younger patients, elderly patients are more likely to have comorbidities, poorer ECOG, are more likely to experience treatment-related toxicity and more often experience dose reductions, which might contribute to less-effective outcome. In four studies comorbidities were evaluated using CCI/or CIRS (cumulative illness rating scale), along with clinical parameters and biomarkers (Saygin et al., 2017; Miura et al., 2017; Liu et al., 2018a; Pardal et al., 2018). One study, that incorporated CCI in a prognostic model, was developed for a general DLBCL population, but provided better discriminative power when tested on the elderly population (Antic et al., 2018). However, these studies are limited, mainly due to their retrospective nature, heterogeneity of the analysed populations, and lack of external validation. Moreover, CCI is not as extensively used worldwide, which may limit the applicability of proposed models (Liu et al., 2018a). Furthermore, proposed models indicated that although the presence of comorbidities is a key prognostic factor of survival, they did not seem to significantly influence the choice of treatment type (Pardal et al., 2018).

This review has some limitations that are mainly due to the process used to search the literature and select the articles. Some potentially important studies might have been missed due to language selection, since we have used English articles only. Despite the potential limitations, our review demonstrates the need for further refinement of models that incorporate clinical, biological, molecular and imaging information into prognostication and clinical decision making.

5. Conclusion

Due to improved treatment options, pathobiology and life expectancy of DLBCL patients, the widely used IPI has been challenged, and a number of new prognostic scores have been proposed. So far, R-IPI and the even more recent NCCN-IPI have shown improved prognostic value compared to IPI in a few independent study populations. Although other models have suggested better discriminative power compared to NCCN-IPI, they have not been externally validated. Furthermore, the majority of proposed models are limited due to their retrospective nature, number of included patients, lack external validation and comparison to other models. It is evident that a vast number of potential prognostic models have been emerging over the recent years, but still there isn't a model that successfully combines the majority of the prognostic important parameters in DLBCL. The model that could be used for a more personalized treatment approach in DLBCL patients is not our present yet, but our future.

Conflict of interest

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References

Saygin, C., Jia, X., Hill, B., Dean, R., Pohlman, B., Smith, M.R., et al., 2017. Impact of comorbidities on outcomes of elderly patients with diffuse large B-cell lymphoma. Am. J. Hematol. 92, 989–996.

Shipp, M.A., Harrington, D.P., Anderson, J.R., Armitage, J.O., Bonadonna, G., Brittinger, G., et al., 1993. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-hodgkin's lymphoma prognostic factors project. N. Engl. J. Med. 329, 987–994.

Ziepert, M., Hasenclever, D., Kuhnt, E., Glass, B., Schmitz, N., Pfreundschuh, M., et al., 2010. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J. Clin. Oncol. 28, 2373–2380.

Hosoda, Y., Hino, N., Motokura, T., 2018. Comparison of prognostic indices in japanese patients with diffuse large B-cell lymphoma in the Yonago Area. Yonago Acta Med. 61, 58–65.

Sehn, L.H., Berry, B., Chhanabhai, M., Fitzgerald, C., Gill, K., Hoskins, P., et al., 2007. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109, 1857–1861.

Zhou, Z., Sehn, L.H., Rademaker, A.W., Gordon, L.I., Lacasce, A.S., Crosby-Thompson, A., et al., 2014. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 123, 837–842.

Melchardt, T., Troppan, K., Weiss, L., Hufnagl, C., Neureiter, D., Tränkenschuh, W., et al., 2015. A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and β2 -microglobulin. Br. J. Haematol. 168, 239–245.

Hong, F., Kahl, B.S., Gray, R., 2013. Incremental value in outcome prediction with gene expression-based signatures in diffuse large B-cell lymphoma. Blood 121, 156–158.
Salles, G., de Jong, D., Xie, W., Rosenwald, A., Chhanabhai, M., Gaulard, P., et al., 2011. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. Blood 117, 7070–7078.
Schmidt-Hansen, M., Berendse, S., Marafioti, T., McNamara, C., 2017. Does cell-of-origin or *MYC*, *BCL2* or *BCL6* translocation status provide prognostic information beyond the International Prognostic Index score in patients with diffuse large B-cell lymphoma treated with rituximab and chemotherapy? A systematic review. Leuk. Lymphoma 58, 2403–2418.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6, e1000100.
Conconi, A., Zucca, E., Roggero, E., Bertoni, F., Bernasconi, A., Mingrone, W., et al., 2000. Prognostic models for diffuse large B-cell lymphoma. Hematol. Oncol. 18, 61–73.
Barrans, S.L., Carter, I., Owen, R.G., Davies, F.E., Patmore, R.D., Haynes, A.P., et al., 2002. Germinal center phenotype and bcl-2 expression combined with the International Prognostic Index improves patient risk stratification in diffuse large B-cell lymphoma. Blood 99, 1136–1143.
Cox, M.C., Nofroni, I., Ruco, L., Amodeo, R., Ferrari, A., La Verde, G., et al., 2008. Low absolute lymphocyte count is a poor prognostic factor in diffuse-large-B-cell-lymphoma. Leuk. Lymphoma 49, 1745–1751.
Wilcox, R.A., Ristow, K., Habermann, T.M., Inwards, D.J., Micallef, I.N., Johnston, P.B., et al., 2011. The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large-B-cell lymphoma. Leukemia 25, 1502–1509.
Tomita, N., Sakai, R., Fujisawa, S., Fujimaki, K., Taguchi, J., Hashimoto, C., et al., 2012. SIL index, comprising stage, soluble interleukin-2 receptor, and lactate dehydrogenase, is a useful prognostic predictor in diffuse large B-cell lymphoma. Cancer Sci. 103, 1518–1523.
Lanic, H., Mareschal, S., Mechken, F., Picquenot, J.M., Cornic, M., Maingonnat, C., et al., 2012. Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. Leuk. Lymphoma 53, 34–42.
Huang, Y.-C., Liu, C.-Y., Lu, H.-J., Liu, H.T., Hung, M.H., Hong, Y.C., et al., 2013. Comparison of prognostic models for patients with diffuse large B-cell lymphoma in the rituximab era. Ann. Hematol. 92, 1513–1520.
Aoki, K., Tabata, S., Yonetani, N., Matsushita, A., Ishikawa, T., 2013. The prognostic impact of absolute lymphocyte and monocyte counts at diagnosis of diffuse large B-cell lymphoma in the rituximab era. Acta Haematol. 130, 242–246.
Batty, N., Ghonimi, E., Feng, L., Fayad, L., Younes, A., Rodriguez, M.A., et al., 2013. The absolute monocyte and lymphocyte prognostic index for patients with diffuse large B-cell lymphoma who receive R-CHOP. Clin. Lymphoma Myeloma Leuk. 13, 15–18.
Nols, N., Mounier, N., Bouazza, S., Lhommel, R., Costantini, S., Vander Borght, T., et al., 2014. Quantitative and qualitative analysis of metabolic response at interim positron emission tomography scan combined with International Prognostic Index is highly predictive of outcome in diffuse large B-cell lymphoma. Leuk. Lymphoma 55, 773–780.
Jung, S.-H., Yang, D.-H., Ahn, J.-S., Kim, Y.K., Kim, H.J., Lee, J.J., 2015. Serum lactate dehydrogenase with a systemic inflammation score is useful for predicting response and survival in patients with newly diagnosed diffuse large B-cell lymphoma. Acta Haematol. 133, 10–17.
Gang, A.O., Pedersen, M., d'Amore, F., Pedersen, L.M., Jensen, B.A., Jensen, P., et al., 2015. A clinically based prognostic index for diffuse large B-cell lymphoma with a cut-off at 70 years of age significantly improves prognostic stratification: population-based analysis from the Danish Lymphoma Registry. Leuk. Lymphoma 56, 2556–2562.
Ho, C.-L., Lu, C.-S., Chen, J.-H., Chen, Y.G., Huang, T.C., 2015. Wu YY. Neutrophil/Lymphocyte ratio, Lymphocyte/Monocyte ratio, and absolute lymphocyte Count/Absolute monocyte count prognostic score in diffuse large B-Cell lymphoma. Medicine (Baltimore) 94, e993.
Kanemasa, Y., Shimoyama, T., Sasaki, Y., Tamura, M., Sawada, T., Omuro, Y., et al., 2017. Beta-2 microglobulin as a significant prognostic factor and a new risk model for patients with diffuse large B-cell lymphoma. Hematol. Oncol. 35, 440–446.
Kong, Y., Qu, L., Li, Y., Liu, D., Lv, X., Han, J., 2016. Predictive significance of a new prognostic score for patients with diffuse large B-Cell lymphoma in the interim-positron emission tomography findings. Medicine (Baltimore) 95, e2808.
Chen, Y., Neelapu, S., Feng, L., Bi, W., Yang, T.H., Wang, M., et al., 2016. Prognostic significance of baseline peripheral absolute neutrophil, monocyte and serum β2-microglobulin level in patients with diffuse large b-cell lymphoma: a new prognostic model. Br. J. Haematol. 175, 290–299.
Xu-Monette, Z.Y., Li, L., Byrd, J.C., Jabbar, K.J., Manyam, G.C., Maria de Winde, C., et al., 2016. Assessment of CD37 B-cell antigen and cell-of-origin significantly improves risk prediction in diffuse large B-cell lymphoma. Blood 128, 3083–3100.
Kobayashi, T., Kuroda, J., Yokota, I., Tanba, K., Fujino, T., Kuwahara, S., et al., 2016. The Kyoto Prognostic Index for patients with diffuse large B-cell lymphoma in the rituximab era. Blood Cancer J. 6 e383–e383.
Montalbán, C., Díaz-López, A., Dlouhy, I., Rovira, J., Lopez-Guillermo, A., Alonso, S., et al., 2017. Validation of the NCCN-IPI for diffuse large B-cell lymphoma (DLBCL): the addition of β2 -microglobulin yields a more accurate GELTAMO-IPI. Br. J. Haematol. 176, 918–928.
Ochi, Y., Kazuma, Y., Hiramoto, N., Ono, Y., Yoshioka, S., Yonetani, N., et al., 2017. Utility of a simple prognostic stratification based on platelet counts and serum albumin levels in elderly patients with diffuse large B cell lymphoma. Ann. Hematol. 96, 1–8.
Kang, J., Yoon, S., Suh, C., 2017. Relevance of prognostic index with β2-microglobulin for patients with diffuse large B-cell lymphoma in the rituximab era. Blood Res. 52, 276.
Sun, F., Zhu, J., Lu, S., Zhen, Z., Wang, J., Huang, J., et al., 2018. An inflammation-based cumulative prognostic score system in patients with diffuse large B cell lymphoma in rituximab era. BMC Cancer 18, 5.
Antic, D., Jelicic, J., Trajkovic, G., Balint, M.T., Bila, J., Markovic, O., et al., 2018. Is it possible to improve prognostic value of NCCN-IPI in patients with diffuse large B cell lymphoma? The prognostic significance of comorbidities. Ann. Hematol. 97, 267–276.
Zhao, P., Zang, L., Zhang, X., Chen, Y., Yue, Z., Yang, H., et al., 2018. Novel prognostic scoring system for diffuse large B-cell lymphoma. Oncol. Lett. 15, 5325–5332.
Matsumoto, K., Fujisawa, S., Ando, T., Koyama, M., Koyama, S., Ishii, Y., et al., 2018. Anemia associated with worse outcome in diffuse large B-cell lymphoma patients: a single-center retrospective study. Turk. J. Haematol. doihttps://doi.org/10.4274/tjh.2017.0437. [Epub ahead of print].
Gao, R., Liang, J.-H., Wang, L., Zhu, H.Y., Wu, W., Cao, L., et al., 2018. Low serum cholesterol levels predict inferior prognosis and improve NCCN-IPI scoring in diffuse large B cell lymphoma. Int. J. Cancer. https://doi.org/10.1002/ijc.31590. [Epub ahead of print].
Advani, R.H., Chen, H., Habermann, T.M., Morrison, V.A., Weller, E.A., Fisher, R.I., et al., 2010. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). Br. J. Haematol. 151, 143–151.
Procházka, V., Pytlík, R., Janíková, A., Belada, D., Sálek, D., Papajík, T., et al., 2014. A new prognostic score for elderly patients with diffuse large B-Cell lymphoma treated with R-CHOP: the prognostic role of blood monocyte and lymphocyte counts is absent. PLoS One 9, e102594.
Miura, K., Konishi, J., Miyake, T., Makita, M., Hojo, A., Masaki, Y., et al., 2017. A host-dependent prognostic model for elderly patients with diffuse large B-Cell lymphoma. Oncologist 22, 554–560.
Candelaria, M., Reynoso-Noverón, N., Ponce, M., Castillo-Llanos, R., Nolasco-Medina, D., Cantú-De-Leon, D., et al., 2018. A prognostic score for survival in patients older than 65 years with Diffuse Large B-Cell Lymphoma. Rev. Invest. Clin. 70, 46–52.
Liu, H., Zhang, C.-L., Feng, R., Li, J.T., Tian, Y., Wang, T., et al., 2018a. Validation and refinement of the age, comorbidities, and albumin index in elderly patients with diffuse large B-Cell lymphoma: an effective tool for comprehensive geriatric assessment. Oncologist 23, 722–729.
Pardal, E., Díez Baeza, E., Salas, Q., García, T., Sancho, J.M., Monzón, E., et al., 2018. A new prognostic model identifies patients aged 80 years and older with diffuse large B-cell lymphoma who may benefit from curative treatment: a multicenter, retrospective analysis by the Spanish GELTAMO group. Am. J. Hematol. 93 (7), 867–873. https://doi.org/10.1002/ajh.25107.
Nicolaides, C., Fountzilas, G., Zoumbos, N., Skarlos, D., Kosmidis, P., Pectasides, D., et al., 1998. Diffuse large cell lymphomas: identification of prognostic factors and validation of the international non-hodgkin's lymphoma prognostic index. Oncology 55, 405–415.
Biccler, J., Eloranta, S., de Nully Brown, P., Frederiksen, H., Jerkeman, M., Smedby, K.E., et al., 2018. Simplicity at the cost of predictive accuracy in diffuse large B-cell lymphoma: a critical assessment of the R-IPI, IPI, and NCCN-IPI. Cancer Med. 7, 114–122.
Olszewski, A.J., Winer, E.S., Castillo, J.J., 2015. Validation of clinical prognostic indices for diffuse large B-cell lymphoma in the National Cancer data Base. Cancer Causes Control 26, 1163–1172.
Hong, J., Park, S., Park, J., Kim, H.S., Kim, K.H., Ahn, J.Y., et al., 2011. Evaluation of prognostic values of clinical and histopathologic characteristics in diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy. Leuk. Lymphoma 52, 1904–1912.
Huang, H.-H., Xiao, F., Chen, F.-Y., Wang, T., Li, J.M., Wang, J.M., et al., 2012. Reassessment of the prognostic value of the International Prognostic Index and the revised International Prognostic Index in patients with diffuse large B-cell lymphoma: a multicentre study. Exp. Ther. Med. 4, 475–480.
Bari, A., Marcheselli, L., Sacchi, S., Marcheselli, R., Pozzi, S., Ferri, P., et al., 2009. Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story. Ann. Oncol. 21, 1486–1491.
Tomita, N., Suzuki, T., Miyashita, K., Yamamoto, W., Motohashi, K., Tachibana, T., et al., 2016. The SIL index is a simple and objective prognostic indicator in diffuse large B-cell lymphoma. Leuk. Lymphoma 57, 2763–2770.
Hong, J., Kim, S.J., Chang, M.H., Kim, J.A., Kwak, J.Y., Kim, J.S., et al., 2017. Improved prognostic stratification using NCCN- and GELTAMO-international prognostic index in patients with diffuse large B-cell lymphoma. Oncotarget 8, 92171–92182.
Yang, Y., Wang, L., Ma, Y., Han, T., Huang, M., 2017. The enhanced international prognostic index for diffuse large B-cell lymphoma. Am. J. Med. Sci. 353, 459–465.
Nakaya, A., Fujita, S., Satake, A., Nakanishi, T., Azuma, Y., Tsubokura, Y., et al., 2016. Enhanced international prognostic index in Japanese patients with diffuse large B-cell lymphoma. Leuk Res Reports 6, 24–26.
Huang, C.E., Chen, Y.Y., Lu, C.H., Chen, P.T., Lee, K.D., Chen, C.C., 2015. Validation of an enhanced International Prognostic Index (NCCN-IPI) in an Asian cohort of patients with diffuse large B cell lymphoma. Ann. Hematol. 94, 1063–1065.
Spiegel, J.Y., Cheung, M.C., Guirguis, H.R., Buckstein, R., 2017. Validation of the NCCN-IPI in both *de novo* and transformed diffuse large B cell lymphoma. Leuk. Lymphoma 58, 214–217.
Liu, T., Chen, L., Pan, J., Pan, L., Hu, J., Ji, Z., et al., 2018b. Retrospective analysis of a new prognostic score for diffuse large B-Cell lymphoma based on interim positron emission tomography-computed tomography. Acta Haematol. 139, 148–157.

Sehn, L.H., 2012. Paramount prognostic factors that guide therapeutic strategies in diffuse large B-cell lymphoma. Hematology Am. Soc. Hematol. Educ. Program (2012), 402–409.
Rosenwald, A., Wright, G., Chan, W.C., Connors, J.M., Campo, E., Fisher, R.I., et al., 2002. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N. Engl. J. Med. 346, 1937–1947.
Dave, S.S., Wright, G., Tan, B., Rosenwald, A., Gascoyne, R.D., Chan, W.C., et al., 2004. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N. Engl. J. Med. 351, 2159–2169.
Lenz, G., Wright, G., Dave, S.S., et al., 2008. Stromal gene signatures in large-B-cell lymphomas. N. Engl. J. Med. 359, 2313–2323 2004.
Alizadeh, A.A., Eisen, M.B., Davis, R.E., Ma, C., Lossos, I.S., Rosenwald, A., et al., 2000. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403, 503–511.
Gutierrez-Garcia, G., Cardesa-Salzmann, T., Climent, F., González-Barca, E., Mercadal, S., Mate, J.L., et al., 2011. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Blood 117, 4836–4843.
Porrata, L.F., Inwards, D.J., Ansell, S.M., Micallef, I.N., Johnston, P.B., Hogan, W.J., et al., 2010. New-onset lymphopenia assessed during routine follow-up is a risk factor for relapse postautologous peripheral blood hematopoietic stem cell transplantation in patients with diffuse large B-cell lymphoma. Biol. Blood Marrow Transplant. 16, 376–383.
Scott, D.W., Wright, G.W., Williams, P.M., Lih, C.J., Walsh, W., Jaffe, E.S., et al., 2014. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood 123, 1214–1217.
Itti, E., Lin, C., Dupuis, J., Paone, G., Capacchione, D., Rahmouni, A., et al., 2009. Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy. J. Nucl. Med. 50, 527–533.
Barrington, S.F., Mikhaeel, N.G., 2016. PET scans for staging and restaging in diffuse large B-Cell and follicular lymphomas. Curr. Hematol. Malig. Rep. 11, 185–195.
Pfreundschuh, M., Kuhnt, E., Trümper, L., Osterborg, A., Trneny, M., Shepherd, L., et al., 2011. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 12, 1013–1022.
Pfreundschuh, M., Trümper, L., Osterborg, A., Pettengell, R., Trneny, M., Imrie, K., et al., 2006. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 7, 379–391.
Pfreundschuh, M., Schubert, J., Ziepert, M., Schmits, R., Mohren, M., Lengfelder, E., et al., 2008. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 9, 105–116.