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Prognostic and therapeutic value of somatic mutations in diffuse large B-cell lymphoma: A systematic review

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL), the most common type of Non-Hodgkin lymphoma (NHL), is a highly heterogeneous and aggressive disease. Regardless of this heterogeneity, all patients receive the same first-line therapy, which fails in 30–40 % of patients, who are either refractory or relapse after remission. With the aim of stratifying patients to improve treatment outcome, different clinical and genetic biomarkers have been studied. The present systematic review aimed to identify somatic mutations that could serve as prognosis biomarkers or as therapeutic target mutations in DLBCL. Regarding their role as prognostic markers, mutations in *CD58* and *TP53* seem the most promising predictors of poor outcome although the combination of different alterations and other prognostic factors could be a more powerful strategy. On the other hand, different approaches regarding targeted therapy have been proposed. Therefore, mutational analysis could help guide treatment choice in DLBCL yet further studies and clinical trials are needed.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin lymphoma (NHL), accounting for 30 %–40 % of all newly diagnosed adult NHL cases (Siegel et al., 2017; Armitage et al., 2017). DLBCL is a high grade mature B-cell neoplasm that originates in lymph nodes or extranodal lymphoid tissue (Li et al., 2018). Even if it is considered as a single entity, it is a remarkably heterogeneous disease, with variable clinical features, morphological and genetic abnormalities, and response to treatment (Swerdlow et al., 2016).

Despite this heterogeneity, the combined chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is nowadays considered the standard first line therapy for all DLBCL patients (Kesavan et al., 2019). Although most patients with DLBCL treated with R-CHOP achieve complete remission, 30–40 % of patients are either refractory to this therapy or relapse after remission, requiring new therapeutic approaches (Coiffier et al., 2010; Coiffier, 2002; Sarkozy and Sehn, 2018). These relapsing or refractory patients present a poor prognosis, therefore, the identification *a priori* of those patients who will not be cured by R-CHOP is one of the current challenges in the diagnosis of DLBCL. In this regard, considerable research has been performed in the last years with the aim of stratifying patients based on prognosis.

So far, the International Prognostic Index (IPI) is one of the most important prognostic tools for survival prediction. This score stratifies

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patients according to intrinsic factors (age, performance status) and the extent and aggressiveness of the disease (stage, presence of extranodal infiltration, lactate dehydrogenase levels) (Project IN-HsLPF, 1993). However, these clinical parameters do not address the underlying biological heterogeneity of DLBCL. Consequently, some limitations remain, such as poor characterization and huge heterogeneity, resulting in difficulties to predict survival; in fact, the utility of IPI in the era of immunochemotherapy has not been established, and the subsequent revisions that have appeared (the R-IPI and the NCCN-IPI) also fail to adequately identify extremely high-risk groups response precisely enough to design risk adapted therapies (Wight et al., 2018).

In recent years the application of gene expression profiling (GEP) to the study of DLBCL was a major advance which further clarified DLBCL heterogeneity and provided a rationale for subdividing cases into groups. The most popular system separates cases of DLBCL according to cell-of-origin into germinal center B-cell like (GCB) and activated B-cell like (ABC) subtypes, the latter having a worse overall prognosis (Alizadeh et al., 2000). Nevertheless, about 10–15 % of cases cannot be classified into any of these two groups. Moreover, although cell-of-origin is useful for predicting outcome, GCB and ABC subtypes remain very heterogeneous with better and worse prognostic subsets within each group (Li et al., 2018).

Finally, the application of next generation sequencing (NGS) technologies in DLBCL has allowed the identification of numerous genetic abnormalities in these neoplasms that can be used as predictive or prognostic biomarkers to assess the risk of treatment failure better than traditional tools (Chapuy et al., 2018; Schmitz et al., 2018; Wright et al., 2020). NGS studies have also found some possible actionable mutations and have confirmed that the ABC and GCB subtypes present characteristic mutational profiles that may explain the difference in gene expression and clinical outcomes (Miao et al., 2019). In spite of these advances, clinical and therapeutic implications of most mutations in DLBCL remain unknown. Therefore, in-depth knowledge of the genetic landscape in DLBCL is needed to identify prognostic and actionable mutations that would allow to perform a risk-adapted guided therapeutic approach.

The present review aimed to identify a panel of somatic mutations that could be used as prognosis biomarkers or as therapeutic target mutations in DLBCL through a systematic search of the literature.

2. Materials and methods

2.1. Search strategy

We performed an exhaustive systematic search in Pubmed database (https://www.ncbi.nlm.nih.gov/pubmed) following the PRISMA protocol to identify studies that analyzed the prognostic/therapeutic value of coding somatic mutations in DLBCL. We used the keywords and subject terms "(somatic mutations OR genetic alterations) AND (diffuse large B cell lymphoma OR DLBCL)" for articles published until 16th of December 2019. All references within the identified studies were then reviewed in order to identify additional matches.

2.2. Inclusion and exclusion criteria

Articles were included if they were independent original studies that supplied information on somatic mutations as prognosis biomarkers or therapeutic target mutations in DLBCL in human population. Articles not published in English, reviews and meta-analyses, letters, comments, methodological articles and studies which used nonstandard oncological treatment were excluded. Additionally, studies that analyzed germinal mutations, non-coding somatic mutations, mitochondrial mutations, IGH-VDJ rearrangements (or other rearrangements), or investigated other diseases or species were also excluded. Each eligible manuscript was assessed independently by three researchers (GM, MLS, PA). Disagreements were solved by consensus.

2.3. Data extraction

Data extracted from each study included: studied genes, mutations detected, pathway in which they were implicated, mutation frequency, sample size, sample characteristics (age, de novo/secondary, received treatment, IPI score, subtype ABC vs GCB), implications of the mutations in DLBCL prognosis (overall survival [OS], progression free survival [PFS], lymphoma-specific survival [LSS], disease-specific survival [DSS], event-free survival [EFS], time-to-progression [TTP], complete remission [CR] or relapse percentage) and whether they were therapeutic target mutations. In order to define associations between somatic mutations and DLBCL outcome, a p value < 0.05 in association with any of the considered endpoints of prognosis was considered.

3. Results

The original search provided a total of 575 records. Out of them, 492 were discarded after abstract revision because they did not meet the required inclusion criteria. The full texts of the remaining 83 studies were examined in detail. Further 55 articles were excluded because they were not focused on somatic mutations as prognosis biomarkers or therapeutic targets in DLBCL. After reviewing the references of the identified articles, 14 additional studies were included. Finally, a total of 42 articles investigating the role of somatic mutations as prognosis biomarkers or therapeutic targets in DLBCL were included (Fig. 1). All of them except one considered mutations in DLBCL as prognosis biomarkers (Chapuy et al., 2018; Schmitz et al., 2018; Leroy et al., 2002; Kerbauy et al., 2004; Iqbal et al., 2007; Young et al., 2008, 2007; Zainuddin et al., 2009; Liu et al., 2010; Stefancikova et al., 2011; Schuetz et al., 2012; Bu et al., 2012; Xu-Monette et al., 2012; Schif et al., 2013; Trinh et al., 2013; Morin et al., 2013; Bertrand et al., 2013; Asmar et al., 2014; Kristensen et al., 2014; Fernández-Rodríguez et al., 2014; Novak et al., 2015; Cen et al., 2015; Schiefer et al., 2015; Dubois et al., 2016; Xu-Monette et al., 2016; Juskevicius et al., 2016; Xia et al., 2017; Cao et al., 2016; Dubois et al., 2017; Xu et al., 2017; Juskevicius et al., 2017; Ennishi et al., 2017; Zlamalikova et al., 2017; Karube et al., 2018; Reddy et al., 2017; Voropaeva et al., 2019; Ramis-Zaldivar et al., 2020; Bolen et al., 2020; Arthur et al., 2018; Møller et al., 2000; Grønbaek et al., 2000), while 8 articles also defined mutations found in DLBCL patients as therapeutic targets or analyzed the frequency of somatic mutations previously defined as therapeutic targets (Bertrand et al., 2013; Schiefer et al., 2015; Dubois et al., 2016, 2017; Xu et al., 2017; Ennishi et al., 2017; Karube et al., 2018; Dubois et al., 2015).

3.1. Prognosis biomarkers

A total of 41 studies analyzing gene mutations as prognosis biomarkers in DLBCL were identified in the systematic search (Supplementary Table S1). The vast majority ($n = 38$) studied the prognostic value of mutations in a unique gene, while 10 of them and other 3 additional studies ($n = 13$) analyzed mutations in a group of genes, in a specific pathway or cluster, or evaluated the combination of gene mutations with diverse genetic alterations (Chapuy et al., 2018; Schmitz et al., 2018; Stefancikova et al., 2011; Asmar et al., 2014; Kristensen et al., 2014; Schiefer et al., 2015; Dubois et al., 2017; Xu et al., 2017; Juskevicius et al., 2017; Karube et al., 2018; Reddy et al., 2017; Bolen et al., 2020; Grønbaek et al., 2000). A subset of studies differentiated DLBCL subtypes when analyzing the impact on prognosis of mutations identified. On the one hand, 15 studies specifically showed results in ABC or non-GC subtype (Chapuy et al., 2018; Schmitz et al., 2018; Iqbal et al., 2007; Young et al., 2008, 2007; Zainuddin et al., 2009; Xu-Monette et al., 2012; Cen et al., 2015; Dubois et al., 2016; Xu-Monette et al., 2016; Xia et al., 2017; Dubois et al., 2017; Ennishi et al., 2017; Reddy et al., 2017; Bolen et al., 2020), from which 10 focused exclusively on single gene mutations (Iqbal et al., 2007; Young et al., 2008, 2007; Zainuddin et al., 2009; Xu-Monette et al., 2012; Cen et al., 2015; Dubois

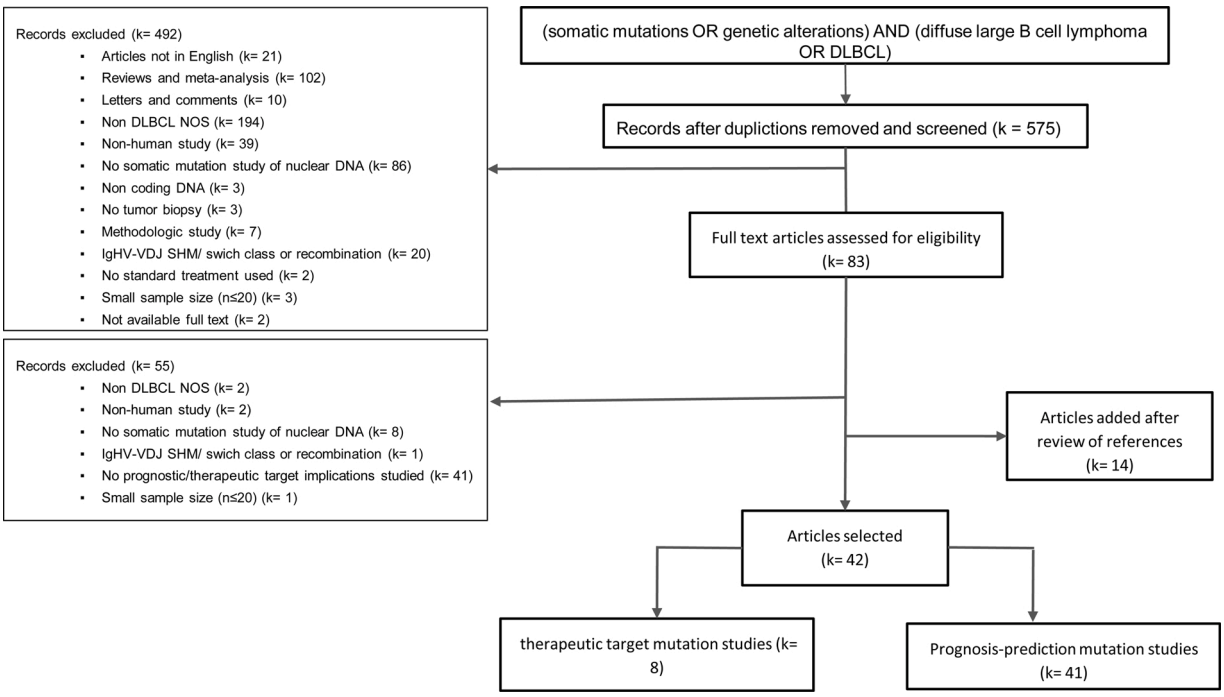

Fig. 1. Flowchart of study selection.

et al., 2016; Xu-Monette et al., 2016; Xia et al., 2017; Dubois et al., 2017; Ennishi et al., 2017; Bolen et al., 2020) and three exclusively on the combination with other genetic alterations (Chapuy et al., 2018; Schmitz et al., 2018; Dubois et al., 2017; Reddy et al., 2017; Bolen et al., 2020) and the remaining two articles studied both (Dubois et al., 2017; Bolen et al., 2020). On the other hand, 15 studies displayed results in GCB subgroup (Chapuy et al., 2018; Schmitz et al., 2018; Iqbal et al., 2007; Young et al., 2008, 2007; Zainuddin et al., 2009; Xu-Monette et al., 2012; Morin et al., 2013; Xia et al., 2017; Juskevicius et al., 2017; Ennishi et al., 2017; Reddy et al., 2017; Bolen et al., 2020; Arthur et al., 2018; Xu-Monette et al., 2015), from which 11 referred solely to single gene mutations (Iqbal et al., 2007; Young et al., 2008, 2007; Zainuddin et al., 2009; Xu-Monette et al., 2012; Morin et al., 2013; Xu-Monette et al., 2016; Xia et al., 2017; Juskevicius et al., 2017; Ennishi et al., 2017; Bolen et al., 2020; Arthur et al., 2018), three focused solely on the combination of gene mutations with other genetic alterations (Chapuy et al., 2018; Schmitz et al., 2018; Reddy et al., 2017; Bolen et al., 2020) and one article analyzed both of them (Bolen et al., 2020).

3.1.1. *Single gene mutations*

Considering DLBCL globally, 36 genes were found to be significantly associated with outcome (Table 1). In most cases, the relationship between gene mutations and prognosis was analyzed by a single study, finding an association with worse outcome in 19 genes (*HERC2*, *KIAA1614*, *ODZ3/TENM3*, *C10orf12*, *DIAPH2*, *SEC14L5*, *BAI1*, *SDK2*, *TRIM2*, *MYO19*, *FBLN2*, *COL12A1*, *ALDH3A2*, *KIF1C*, *HEPH*, *FGFRL1*, *KLHL14*, *ZFAT* and *SETD5*) (Novak et al., 2015; Reddy et al., 2017) and with better outcome in two genes (*NF1*, *HRAS*) (Reddy et al., 2017). The other 15 genes were examined by at least two studies, all of them displaying discordant results: worse outcome- or non-significant results (*CD58, BCL2, MYD88, KLHL6, FOXO1, MYC, CD79B, PIM1, CDKN2A, PAX5, TP53*); better outcome- or non-significant results (*EZH2, BCL6, SOCS1*); and conflicting results (better, worse or no-significant differences in outcome) (*SGK1*). For 13 of these genes the majority of studies performed did not show any association with prognosis: *BCL2* (7 out of 9 studies) (Schuetz et al., 2012; Novak et al., 2015; Cao et al., 2016; Juskevicius et al., 2017; Ennishi et al., 2017; Karube et al., 2018; Reddy et al., 2017), *BCL6* (4 out of 5) (Juskevicius et al., 2016; Cao et al., 2016; Karube et al., 2018; Reddy et al., 2017), *CD79B* (6 out of 7) (Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020), *CDKN2A* (2 out of 3) (Juskevicius et al., 2016; Karube et al., 2018), *EZH2* (5 out of 6) (Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020), *KLHL6* (2 out of 3) (Juskevicius et al., 2016; Reddy et al., 2017), *MYC* (7 out of 9) (Novak et al., 2015; Xu-Monette et al., 2016; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Ennishi et al., 2017; Karube et al., 2018), *MYD88* (7 out of 9) (Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Xu et al., 2017; Juskevicius et al., 2017; Karube et al., 2018; Reddy et al., 2017; Bolen et al., 2020), *PIM1* (6 out of 7) (Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020), *SOCS1* (4 out of 5) (Schif et al., 2013; Juskevicius et al., 2017; Karube et al., 2018; Reddy et al., 2017), *PAX5* (1 out of 2) (Juskevicius et al., 2016), *FOXO1* (3 out of 5) (Juskevicius et al., 2016; Karube et al., 2018; Reddy et al., 2017), and *SGK1* (2 out of 4) (Juskevicius et al., 2016, 2017). Among the lacking two genes, *TP53* was the most often analyzed: 10 articles showed statistically significant association with adverse prognosis (Leroy et al., 2002; Kerbauy et al., 2004; Young et al., 2008, 2007; Zainuddin et al., 2009; Liu et al., 2010; Xu-Monette et al., 2012; Cao et al., 2016; Zlamalikova et al., 2017; Ramis-Zaldivar et al., 2020), while 10 studies had non-significant results (Asmar et al., 2014; Kristensen et al., 2014; Novak et al., 2015; Juskevicius et al., 2016, 2017; Karube et al., 2018; Reddy et al., 2017; Voropaeva et al., 2019; Bolen et al., 2020; Møller et al., 2000). Besides, two additional studies explored not only mutations but also deletions in *TP53* as prognosis biomarkers, finding that the presence of any of these was a signal of unfavorable prognosis in R-CHOP treated patients (Stefancikova et al., 2011; Schiefer et al., 2015). In addition, *CD58* was the only other gene among those studied by more than 3 studies for which at least half of the studies supported an association with outcome (2 out of 4 found association with worse outcome) (Novak et al., 2015; Cao et al., 2016; Karube et al., 2018; Reddy et al., 2017).

Regarding DLBCL subtypes, 6 genes were found to show significant association with outcome in ABC/non-GC patients: *BCL6* (Iqbal et al., 2007) and *CD79B* (Dubois et al., 2017) correlated with favorable prognosis; and *GNA13* (Dubois et al., 2016), *PRDM1* (Xia et al., 2017),

Table 1
Mutations in single genes associated with prognosis in DLBCL.

Type	Pathway	Gene	Frequency (%)	Prognosis	References
DLBCL	Apoptosis and autophagy	*MYC*	4.5–5.5	↓	(Reddy et al., 2017; Ramis-Zaldivar et al., 2020)
			5.3–33.3	n.s.	(Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Ennishi et al., 2017; Karube et al., 2018); (Xu-Monette et al., 2016)*
		BCL2	8–10.3	↓	(Juskevicius et al., 2016); (Bolen et al., 2020)*
			4.1–37	n.s.	(Schuetz et al., 2012; Novak et al., 2015; Cao et al., 2016; Juskevicius et al., 2017; Ennishi et al., 2017; Karube et al., 2018; Reddy et al., 2017)
	B-cell recept/ (BCR) /Toll-like recept/ (BCR-TLR) signaling pathway	*MYD88* L265P	10	↓	(Fernández-Rodríguez et al., 2014)*
			6.6	n.s.	(Juskevicius et al., 2017)
		MYD88	11.8–24	n.s.	(Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Karube et al., 2018; Reddy et al., 2017; Bolen et al., 2020)
		CD79B	5.0	↓	(Reddy et al., 2017)
			5.3–25.6	n.s.	(Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020)
		KLHL6	8	↓	(Karube et al., 2018)*
			6.8–7.7	n.s.	(Juskevicius et al., 2016; Reddy et al., 2017)
	B-cell diffferentiation	*BCL6*	61	↑	(Iqbal et al., 2007)
			4.7–6	n.s.	(Cao et al., 2016; Karube et al., 2018; Reddy et al., 2017)
			0	n.a.	(Juskevicius et al., 2016)
		PAX5	5.7	↓	(Reddy et al., 2017)
			0	n.a.	(Juskevicius et al., 2016)
	DNA damage	*TP53*	8.9–23	↓	(Leroy et al., 2002; Kerbauy et al., 2004; Young et al., 2008; Liu et al., 2010; Xu-Monette et al., 2012; Cao et al., 2016)*; (Young et al., 2007; Zainuddin et al., 2009; Zlamalikova et al., 2017; Ramis-Zaldivar et al., 2020)
			12.3–25.6	n.s.	(Kristensen et al., 2014; Novak et al., 2015; Juskevicius et al., 2016, 2017; Karube et al., 2018; Reddy et al., 2017); (Asmar et al., 2014; Voropaeva et al., 2019; Møller et al., 2000)* ; (Bolen et al., 2020)* †
		TP53 mut/ del	28.3–31.7	↓	(Schiefer et al., 2015)*; (Stefancikova et al., 2011) (treated with R-CHOP)
		CDKN2A	9.08	↓	(Reddy et al., 2017)
			4	n.s.	(Karube et al., 2018)
			0	n.a.	(Juskevicius et al., 2016)
	Epigenome/Chromatin modifier	*ADGRB1*	5.9	↓	(Novak et al., 2015)
			6.0	↑	(Reddy et al., 2017)
		EZH2	3.1–13.2	n.s.	(Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020)
			0	n.a.	(Juskevicius et al., 2016)
	Extracellular matrix organization	*SETD5*	3.2	↓	(Reddy et al., 2017)
		FBLN2	5.9	↓	(Novak et al., 2015)
		COL12A1	5.9	↓	(Novak et al., 2015)
	Immune response	*CD58*	2.8–5.1	↓	(Cao et al., 2016)*; (Reddy et al., 2017)
			5.9–10.7	n.s.	(Novak et al., 2015; Karube et al., 2018)
		HERC2	15.7	↓	(Novak et al., 2015)
		TRIM2	5.9	↓	(Novak et al., 2015)
	JAK-STAT pathway	*SOCS1*	12.8	↑	(Juskevicius et al., 2016)
			9.7–27.6	n.s.	(Schif et al., 2013; Juskevicius et al., 2017)*; (Karube et al., 2018; Reddy et al., 2017)
		PIM1	17.3	↓	(Reddy et al., 2017)
			9.2–30.8	n.s.	(Novak et al., 2015; Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Bolen et al., 2020)
	MAP kinase signaling	*HRAS*	1.9	↑	(Reddy et al., 2017)
		NF1	3.4	↑	(Reddy et al., 2017)
	NOTCH pathway		7	↓	(Karube et al., 2018) *
		SGK1	7.7	↑	(Reddy et al., 2017)
			5.3–10.7	n.s.	(Juskevicius et al., 2016, 2017)
	PI3K-AKT signaling	*FOXO1*	3.9–8.6	↓	(Trinh et al., 2013)*; (Novak et al., 2015)
			2.6–10.7	n.s.	(Juskevicius et al., 2016; Karube et al., 2018; Reddy et al., 2017)
	Rho GTPases signaling	*DIAPH2*	5.9	↓	(Novak et al., 2015)
	Tryptophan Metabolism	*ALDH3A2*	5.9	↓	(Novak et al., 2015)
	Transmembrane transport of small molecules	*HEPH*	5.9	↓	(Novak et al., 2015)
	Vesicle-mediated transport	*KIF1C*	5.9	↓	(Novak et al., 2015)
	VEGF signaling pathway	*FGFRL1*	5.9	↓	(Novak et al., 2015)
	–	*ZFAT*	4.0	↓	(Reddy et al., 2017)
	–	*KLHL14*	5.5	↓	(Reddy et al., 2017)
	–	*TENM3*	7.8	↓	(Novak et al., 2015)
	–	*KIAA1614*	9.8	↓	(Novak et al., 2015)
	–	*SEC14L5*	5.9	↓	(Novak et al., 2015)
	–	*SDK2*	5.9	↓	(Novak et al., 2015)
	–	*MYO19*	5.9	↓	(Novak et al., 2015)
	–	*LCOR*	5.9	↓	(Novak et al., 2015)
	B-cell diffferentiation	*BCL6*	44	↑	(Iqbal et al., 2007)
		PRDM1	26	↓	(Xia et al., 2017)

(*continued on next page*)

Table 1 (*continued*)

Type	Pathway	Gene	Frequency (%)	Prognosis	References
ABC-DLBCL/ non-GCB-DLBCL	BCR signaling pathway	*CD79B*	28.1	↑	(Dubois et al., 2017)
			25	n.s.	(Bolen et al., 2020)
	DNA damage	*TP53*	17.8	↓	(Xu-Monette et al., 2012)
			14.5−24	n.s.	(Young et al., 2007; Zainuddin et al., 2009; Bolen et al., 2020); (Young et al., 2008)*
	NF-κB Signaling	*TNFAIP3*	11.1	↓	(Dubois et al., 2016) †
			29.5	n.s.	(Cen et al., 2015)
	PI3K-AKT signaling	*GNA13*	9.3	↓	(Dubois et al., 2016) †
GCB-DLBCL	DNA damage	*TP53*	10.6−34	↓	(Zainuddin et al., 2009; Xu-Monette et al., 2012); (Young et al., 2008)*
			19−30	n.s.	(Young et al., 2007; Bolen et al., 2020)
		ATM	15.6	↓	(Juskevicius et al., 2017)

n.s.: non-significant; n.a.: not available.
* Multivariate analysis.
† FDH correction.

TP53 (Xu-Monette et al., 2012) and *TNFAIP3* (Dubois et al., 2016) correlated with worse prognosis. However, *TP53*, *CD79B* and *TNFAIP3* genes, which were the only ones analyzed by more than one study, showed also no significant results: *TP53* was not associated with prognosis in four out of five articles (Young et al., 2008, 2007; Zainuddin et al., 2009; Bolen et al., 2020) and both *CD79B* (Bolen et al., 2020) and *TNFAIP3* (Cen et al., 2015) did not show any association in one out of two articles. Considering GCB patients, two genes were associated with unfavorable outcome, *TP53* in three out of five articles (Young et al., 2008; Zainuddin et al., 2009; Xu-Monette et al., 2012) and *ATM* in one study (Juskevicius et al., 2017).

3.1.2. Pathway or multiple-gene related mutations

Thirteen articles described a significant association between somatic mutations in multiple-genes/specific pathway or the combinations of different mutations with other genetic alterations and survival in DLBCL (Table 2). For instance, two studies found that patients with disruption of CDKN2A and p53 pathways concurrently had significantly shorter survival than patients with disruption of one or no pathways (Karube et al., 2018; Grønbaek et al., 2000). Other work, analyzing not only genetic *TP53* mutations but also epigenetic variations, discovered that the double hit *MIR34A* methylation and *TP53* mutation was an independent factor for survival in DLBCL patients, even after correction for multivariate analysis; however, neither methylation of *MIR34A* nor *TP53* mutation alone influenced survival (Asmar et al., 2014). Another study found that TNFR pathway was more frequently mutated in patients who did not achieve complete remission after treatment, while BCR pathway mutations were associated with shorter PFS in the subgroup of patients who reached complete remission (Xu et al., 2017). Finally, *CREBBP* and/or *EP300* mutations were associated with poor survival in a multivariate analysis (Juskevicius et al., 2017); even though neither of these genes had been associated individually (Juskevicius et al., 2016; Cao et al., 2016; Juskevicius et al., 2017; Karube et al., 2018; Reddy et al., 2017).

On the other hand, Schmitz et al. described diverse subtypes of DLBCL based on their genomic alterations: EZB subtype, characterized by *EZH2* mutations and/or *BCL2* translocations, and BN2 genetic subtype, characterized by *BCL6* fusions or/and *NOTCH2* mutations, displayed improved survival; N1 subtype, characterized by *NOTCH1* mutations, and MCD subtype, characterized by *MYD88* L265 P + *CD79B* mutations, showed deteriorated survival (Schmitz et al., 2018). However, Bolen et al. tried to validate these classifications using an approximation of EZB, BN2, N1 and MCD clusters using each cluster's founder alterations (*EZH2* or *BCL2*; *BCL6* or *NOTCH2*; *NOTCH1*; and *MYD88* L265 P or *CD79B*, respectively), but they did not observe any difference in prognosis among any of the four mutational subgroups (Bolen et al., 2020). Likewise, Chapuy et al. described 6 different clusters (C0-C5) based on their genetic alterations and established a prognosis based on this clustering: C3 (defined by GCB-DLBCLs with *BCL2* structural variants and alterations of *PTEN* and epigenetic enzymes) and C5 (major components being *BCL2* gain, concordant *MYD88* L265 P/*CD79B* mutations, and additional mutations of *ETV6*, *PIM1*, *GRHPR*, *TBL1XR1*, and *BTG1*) presented a poorer prognosis; while C1 (defined by ABC-DLBCLs with genetic features of an extrafollicular, possibly marginal zone origin) and C4 (defined by GCB-DLBCLs with distinct alterations in BCR/PI3K, JAK/STAT, and BRAF pathway components and multiple histones) and C0 (not otherwise defined) clusters having a better prognosis. Besides, they discovered that C3/C5 and C2 groups separately were significantly associated with worse outcome comparing to C0/C1/C4 patients (Chapuy et al., 2018). Later, Bolen et al. applied the non-negative matrix factorization (NMF) clustering algorithm to the set of mutations overlapping with those reported by Chapuy et al. to recreate the Chapuy classification, resulting in six clusters G0-G5 equivalent to C0-C6 clusters of Chapuy's study respectively. G2, G3 and G5 (equivalent to Chapuy's C2, C3 and C5) showed significantly worse prognosis when compared with clusters G0, G1 and G4 (Chapuy's C0, C1 and C4, respectively) (Bolen et al., 2020).

Finally, Reddy et al. proposed a genomic risk model in DLBCL based on combinations of genetic and expression features and validated their predictive modeling approach using an independent test set (20 % of the data), which was able to distinguish patients with high versus low risk of death. In fact, it was also able to discern patients with significantly distinct outcomes within risk groups that are known to influence survival: cell of origin, double expression of MYC and BCL2, and IPI (Reddy et al., 2017). Bolen et al. also used this genomic risk model to test its utility as prognosis tool but after correcting for COO, the model was not significantly associated with prognosis (Bolen et al., 2020).

3.2. Therapeutic targets

We identified eight articles proposing a series of 29 genes as therapeutic targets of drugs that could potentially be used in DLBCL (Bertrand et al., 2013; Schiefer et al., 2015; Dubois et al., 2016, 2017; Xu et al., 2017; Ennishi et al., 2017; Karube et al., 2018; Dubois et al., 2015) (Table 3). In order to identify therapeutic targets for the identified genomic alterations, different strategies were followed: seven studies proposed candidate drugs against somatic mutations based on previous literature, whereas one study performed *in silico* analyses using the software Cancer Genome Interpreter (https://www.cancergenomeinterpreter.org/) (Karube et al., 2018). From the 29 proposed genes, 16 presented only one associated candidate type of drugs while 13 were described as targets of diverse drugs. Similarly, some of the proposed drugs were linked to more than one actionable gene alteration.

Among them, three combinations of mutated genes and targeted drugs were proposed by more than two studies: three studies proposed BCL2 inhibitors for *BCL2* mutants (Schiefer et al., 2015; Dubois et al., 2016; Ennishi et al., 2017), three studies proposed EZH2 inhibitors for *EZH2* mutants (Dubois et al., 2016; Karube et al., 2018; Dubois et al.,

Table 2
Pathway / multiple-gene related mutations associated with prognosis in DLBCL.

Pathway / subtype / risk model	Group of genes	Frequency (%)	Prognosis	References
DNA damage	*TP53* mut/*CDKN2A* del	35.3	↓	(Karube et al., 2018) *
	TP53 mut/ *CDKN2A* del /*CDKN2A* meth	38.2	↓	(Grønbaek et al., 2000)
	MIR34A meth/*TP53* mut	6	↓	(Asmar et al., 2014)*
B-cell recept/ (BCR) /Toll-like recept/ (BCR-TLR) signaling pathway	*CARD11/LYN/CD79A/CD79B*	25.5	↓	(Xu et al., 2017)
	MYD88	18.2	↓	(Xu et al., 2017)
	TRAF2/TNFAIP3	14.5	↓	(Xu et al., 2017)
NOTCH signaling	*NOTCH2/ NOTCH1/ FBXW7/ SGK1*	19.3	↓	(Karube et al., 2018) *
Epigenome/ Chromatin modifier	*CREBBP mut/EP300* mut	18	↓	(Juskevicius et al., 2017)*
DLBCL ABC JAK-STAT + NF-κB	*MYD88* L265 P + *CD79B* (vs MYD88 L265 P + CD79B no mut)	14.9	↑	(Dubois et al., 2017)
EZB subtype	*EZH2* mut/*BCL2* transl	12	↑	(Schmitz et al., 2018)
		20	n.s. #	(Bolen et al., 2020)
N1 subtype	*NOTCH1* mut	3.3	↓	(Schmitz et al., 2018)
		2.4	n.s.#	(Bolen et al., 2020)
BN2 subtype	*BCL6* fusions/*NOTCH2* mut	17.1	↑	(Schmitz et al., 2018)
		11.4	n.s. #	(Bolen et al., 2020)
MCD subtype	*MYD88* L265 P/*CD79B* mut	12.4	↓	(Schmitz et al., 2018)
		13.1	n.s. #	(Bolen et al., 2020)
Reddy-Genomic risk model	High risk (HR): MYC & MYC-high / ZFAT / ABC DLBCL & KLHL14 / BCL2-high & BIRC6 / MYC-high & CDKN2A / BCL2-high & GNA13 / BCL2-high & TP53 / SETD5 / BCL2-high & PIM1 & MYD88 / MYC-high & CARD11 / MYC-high & ABC DLBCL & MLL2 / MYC-high & BCL2-high & HIST1H1E / CD79B & PIM1 / BCL2-high & ABC DLBCL & HIST1H1E / BCL2-high & MCL1 / ABC DLBCL & SPEN / KLHL14 & PIM1, MSH2, NC/1, ABC DLBCL & CDKN2A, BCL2-high & MYD88 & MLL2, DNMT3A / BCL2-high & MLL3 / BCL2-high & BTG1 Low Risk (LR): CHD1, GCB DLBCL & B2M / SGK1 / GNAS / ABC DLBCL & ZEB2, GCB DLBCL & MT/ / ABC DLBCL & DDX10 / ABC DLBCL & CREBBP, ABC DLBCL & ATM, TNFRSF14 & MLL2, GCB DLBCL & EZH2 / NF1 / GCB DLBCL & MYD88 / GCB DLBCL & ARID5B / GCB DLBCL & CD70	52.9–56.3 (HR)	↓	(Reddy et al., 2017)
		29.4 (HR)	n.s. &	(Bolen et al., 2020)
C0 cluster	without defined genetic drivers	4%	↑	(Chapuy et al., 2018) *
C1 cluster	*BCL6 / BCL10 / TNFAIP3 / UBE2A / CD70/ B2M / ZEB2 / NOTCH2 / TMEM30A / FAS / TP63 / ZEB2 / HLA-B / SPEN* /PD-L1-ligands / CN gain 5q/p	21 %	↑	(Chapuy et al., 2018) *
C2 cluster	TP53 alt / CNAs	21.2 %	n.s.	(Chapuy et al., 2018) *
C3 cluster	*BCL2 alt / CREBBP/ EZH2 / KMT2D / TNFRSF14 / HVCN1 / IRF8 / GNA13 / MEF2B / PTEN* alt	18.1 %	↓	(Chapuy et al., 2018) *
C4 cluster	*SGK1 / HIST1H1E / NFKBIE / BRAF / CD38 / NFKBIA / CD58 / HIST1H2BC / STAT3 / HIST1H1D / HIST1H1B / ETS1 / TOX / HIST1H2AM / HIST1H2BK / RHOA / ACTB / LTB / SF3B1 / CARD11 / HIST1H2AC*	16.9 %	↑	(Chapuy et al., 2018) *
C5 cluster	CN-gain 18p/q / CN-gain 3q/p / CD79B / *MYD88 / ETV6 / PIM1* / CN-loss 17q25.1 / *TBL1XR1* / CN-gain 19q13,42 / *GRHPR / ZC3H12A* / CN-loss 19p13.2 /CN-gain 19q / *HLA-A / BTG1 / PRDM1*	21 %	↓	(Chapuy et al., 2018) *
C3/C5 vs C0/C1/C4			↓	(Chapuy et al., 2018) *
C2 vs C0/C1/C4			↓	(Chapuy et al., 2018) *
G2/3/5 vs G0/1/4[$]			↓	(Bolen et al., 2020)

* Multivariate analysis; n.s.: non-significant.
& Mutational model generated by Reddy et al modified.
# Clusters were approximated using the seed mutations: EZB - EZH2 / BCL2; BN2 - BCL6 / NOTCH2; N1 - NOTCH1; MCD - MYD88, L265 P / CD79B.
$ Clusters were approximated by application of non-negative matrix fact/ization (NMF) to the GOYA FMI dataset and selecting five clusters (G1-G5).

Table 3
Targeted drugs and actionable mutations in DLBCL.

Gene	Mutation	Drug	Reference
APC	–	Tankyrase inhibitor	(Karube et al., 2018)
ARID1A	–	EZH2 inhibitor	(Karube et al., 2018)
	–	PARP inhibitor	(Karube et al., 2018)
BCL2	–	BCL2 inhibitor (BH3 mimetics)	(Dubois et al., 2016)
	–	BCL2 inhibitor (BH3 mimetics)	(Schiefer et al., 2015)
	–	BCL2 inhibitor (venetoclax)	(Ennishi et al., 2017)
BRAF	inframe deletions (L485X, P490X)	Pan-RAF inhibitor	(Karube et al., 2018)
	–	BRAF inhibitor	(Dubois et al., 2016)
BRCA2	–	PARP inhibitor (Olaparib, Rucaparib)	(Karube et al., 2018)
	–	PD1 Antibody	(Karube et al., 2018)
	–	Platinum (Chemotherapy)	(Karube et al., 2018)
CARD11/TNFAIP	–	Decreased activity of ibrutinib and sotrastaurin (PKCi)	(Dubois et al., 2016)
CD70	–	Anti-CD70 antibody/ CD70specific T-cells	(Bertrand et al., 2013)
CD79B	–	BTK inhibitor (ibrutinib)	(Karube et al., 2018)
	–	BTK inhibitor	(Dubois et al., 2016)
CDKN2A	–	CDK4/6 inhibitor	(Karube et al., 2018)
	–	AURKA-VEGF inhibitor (Ilorasertib)	(Karube et al., 2018)
CREBBP	–	HDAC inhibitor	(Dubois et al., 2016)
EP300	–	HDAC inhibitor	(Dubois et al., 2016)
EZH2	Y641X, A677X	EZH2 inhibitor (EPZ-005,687)	(Karube et al., 2018)
	Y641 F,A677X	EZH2 inhibitor (EPZ-005,687, EPZ-6438)	(Karube et al., 2018)
	–	EZH2 inhibitor (EPZ-6438)	(Karube et al., 2018)
	–	EZH2 inhibitor	(Dubois et al., 2016)
	EZH2 + mutant-like IHC methylation profiles	EZH2 inhibitor	(Dubois et al., 2015)
IRF4	–	Lenalidomide	(Dubois et al., 2016)
KIT	D816Y, D816 F, D816V	BCR-ABL inhibitor 2nd gen (Dasatinib)	(Karube et al., 2018)
KRAS	–	CDK4/6 inhibitor	(Karube et al., 2018)
	–	Defactinib (Pan-kinase inhibitor)	(Karube et al., 2018)
	–	FAK inhibitor	(Karube et al., 2018)
	–	FAS inhibitor	(Karube et al., 2018)
	–	HSP90 inhibitor (in combination)	(Karube et al., 2018)
	–	JAK/TBK1/IKKε inhibitor	(Karube et al., 2018)
	–	MEK inhibitor (Selumetinib)	(Karube et al., 2018)
	–	PI3K pathway inhibitor	(Karube et al., 2018)
	–	PI3K pathway inhibitor + MAPK pathway inhibitor	(Karube et al., 2018)
MTOR	L1460 P, S2215Y, R2505P	Sirolimus (MTOR inhibitor)	(Karube et al., 2018)
MYC	–	BET inhibitor	(Dubois et al., 2016)
	–	MYC inhibitor	(Ennishi et al., 2017)
MYD88	–	IRAK1/4 inhibitor	(Xu et al., 2017)
	–	BTK inhibitor (ibrutinib)	(Dubois et al., 2016)
	–	BTK inhibitor (ibrutinib)	(Xu et al., 2017)
MYD88+CD79B	MYD88 (L265 P) + CD79B oncogenic mutation	BTK inhibitor (ibrutinib)	(Karube et al., 2018)
	–	BTK inhibitor (ibrutinib)	(Dubois et al., 2016)
MYD88 +no alterations in CARD11/ TNFAIP3	–	BTK inhibitor (ibrutinib)	(Dubois et al., 2017)
NOTCH1	activating mutation (missense in TAD or truncating in Cterm domain)	Gamma secretase inhibitor	(Karube et al., 2018)
	activating mutation (missense in TAD or truncating in Cterm domain)	NOTCH1 inhibitor (OMP-52M51)	(Karube et al., 2018)
	–	NOTCH inhibitor	(Dubois et al., 2016)
NOTCH2	activating mutation (missense in TAD or truncating in Cterm domain)	Gamma secretase inhibitor (Mk-0752)	(Karube et al., 2018)
	activating mutation (missense in TAD or truncating in Cterm domain)	NOTCH2 inhibitor (OMP-59R5)	(Karube et al., 2018)
	–	NOTCH inhibitor	(Dubois et al., 2016)
PIK3CA	–	PI3K pathway inhibitor	(Karube et al., 2018)
	–	PIK3CA inhibitor	(Karube et al., 2018)
PIK3R1	–	AKT inhibitor	(Karube et al., 2018)
PIM1	–	PIM inhibitor	(Dubois et al., 2016)
SOCS1	–	JAK/STAT inhibitor	(Dubois et al., 2016)
STAT6	–	JAK/STAT inhibitor	(Dubois et al., 2016)
TNFAIP3	–	NFKB inhibitor	(Dubois et al., 2016)
	–	proteasome inhibitors (bortezomib and carfilzomib)	(Xu et al., 2017)
TP53	R248Q, R175H	HSP90 inhibitor	(Karube et al., 2018)
	–	ATR inhibitor (AZD6738)	(Karube et al., 2018)
	–	WEE1 inhibitor (MK-1775)	(Karube et al., 2018)
	–	Amylin analogue (Pramlintide)	(Karube et al., 2018)
XPO1	–	SINE	(Dubois et al., 2016)

2015), and four studies proposed the BTK inhibitor ibrutinib for *MYD88* mutants (Dubois et al., 2016, 2017; Xu et al., 2017; Karube et al., 2018).

4. Discussion

The heterogeneity of DLBCL confers variable clinical outcome to patients with DLBCL treated with R-CHOP. Consequently, the identification of more efficient prognostic markers and therapeutic targets is necessary. To date, many genetic alterations have been involved in the pathogenesis of DLBCL. Nevertheless, few of those alterations have been described as prognostic markers or therapeutic targets. Therefore, this systematic review focuses on key mutations that could help elucidate the prognosis of DLBCL or individualize the treatment. This search identified 40 single genes and different combinations associated with prognosis and 29 genes that could serve as therapeutic targets.

4.1. Prognostic value of genetic alterations

Considering the studies that analyzed single genes in all DLBCL patients as a whole, most mutated genes with significant prognostic implications (n = 21) were studied only once and, thus, these results need validation before their real value as prognostic factors can be confirmed. Among these, *HERC2* mutations, which presented a high frequency among DLBCL patients (15.7 % of patients) and were associated with worse outcome (Novak et al., 2015), deserve special mention. HERC2 leads to the recruitment of BRCA1 at DNA damage sites (Bekker-Jensen et al., 2010) for its repair, and high HERC2 expression was found to be associated with worse prognosis in other neoplasms, such as non-small-cell lung cancer (Bonanno et al., 2016). Therefore, although further studies are needed, it should be considered as potential prognosis biomarker.

The other 15 genes were studied at least twice. However, all of them presented discordant results among studies. In fact, available data as a whole seems to support a lack of prognostic significance for 13 of these genes due to the fact that the majority of studies performed did not show any association with prognosis: *BCL2*, *BCL6*, *CD79B*, *CDKN2A*, *EZH2*, *KLHL6*, *MYC*, *MYD88*, *PIM1*, *SOCS1*, *PAX5*, *FOXO1*, and *SGK1*. However, some aspects must be taken into consideration. For instance, the very diverse mutational frequency of *BCL6* among studies is very remarkable, ranging from 0 %–6 % in no-significant studies (Juskevicius et al., 2016; Cao et al., 2016; Karube et al., 2018; Reddy et al., 2017) to 61 % in the article where it was associated with outcome (Iqbal et al., 2007), which could be contributing to the discordance in results. Even though Igbal et al. included 8.6 % of patients classified as PMBL, which are characterized by higher mutational frequency of *BCL6*, the frequency of *BCL6* mutations in the rest of subgroups was also higher than in the other studies. On the other hand, *PAX5* mutations were only studied by two different studies, one showed association with worse outcome (Reddy et al., 2017), whereas the other one did not. Nevertheless, the latter was performed in a much smaller sample (n = 39 vs 1001) and its mutational frequency was of 0%, explaining the lack of significance. Similarly, *CDKN2A* was only studied in three studies and being found associated with prognosis in the study with the largest population (n = 1001). Given its relatively low frequency of mutation (0–9.08 %), a high number of patients may be needed in order to detect its effect on prognosis. Therefore, further studies would be needed to confirm or discard their role in prognosis.

Other factors to take into account are that differences on prognosis significance among studies may also lay in the different prognosis endpoints analyzed in each study or in the specific effect of each mutation on the functionality of the gene. In this line, although Xu-Monette et al. confirmed the lack of association of *MYC* mutations with prognosis taking into account all mutations overall, they described a group of mutations (S62, S67, P79, R83, A141, S175 and A 185 mutations) associated with favorable prognosis, and others (missense mutations at T58 and F138, which were involved in increased Myc stability, gain-of-function and reduced response to apoptosis in vitro) with significantly poorer survival. In addition, *MYD88* L265 P was associated with unfavorable prognosis in a multivariate analysis (Fernández-Rodríguez et al., 2014) and, although this association was not confirmed in another study (Juskevicius et al., 2017), it could be attributed to the low number of *MYD88* L265P-mutated cases (n = 5) included in the survival analysis.

On the other hand, *CD58* and *TP53* are the only two genes among those studied by more than 3 studies for which at least half of the studies support an association with outcome. The remaining genes not mentioned above, were only found associated with prognosis in one or two studies and were found not associated in more studies, including analyses with very large sample sizes. Thus, this two are the most promising single genes for prognostic stratification.

First, CD58 activates T cells and natural killer (NK) cells by its adhesion to CD2 receptor on their surface. Mutations in *CD58* inducing a decrease in CD58 protein levels impede cytolysis of DLBCL cells (Miao et al., 2019). Prognostic significance of *CD58* mutations was studied by 4 articles, two of them finding association with worse prognosis (Cao et al., 2016; Reddy et al., 2017), one of them even independently of other prognostic factors (Cao et al., 2016). The negative studies, however, were performed using smaller sample sizes, which could serve as explanation for not finding significant results (Novak et al., 2015; Karube et al., 2018). Therefore, detecting *CD58* mutations could lead to better stratification of patients with worse prognosis for whom immunotherapy could become an alternative therapy.

Finally, *TP53*, which is a tumor suppressor gene and regulates cell division by keeping cells from growing and proliferating in an uncontrolled way, was the most frequently studied gene in the articles included in this review. Loss of function of *TP53* either by mutations or deletion is a well-known prognostic biomarker in many hematological neoplasms, and in some cases such as in acute myeloid leukemia and chronic lymphocytic leukemia, the loss of TP53 activity can guide treatment strategy (Campo et al., 2018). However, the prognostic value of *TP53* mutations in DLBCL is still controversial: some articles indicated negative prognostic implications (Leroy et al., 2002; Kerbauy et al., 2004; Young et al., 2008, 2007; Zainuddin et al., 2009; Liu et al., 2010; Xu-Monette et al., 2012; Cao et al., 2016; Zlamalikova et al., 2017; Ramis-Zaldivar et al., 2020), while others found no association (Asmar et al., 2014; Kristensen et al., 2014; Novak et al., 2015; Juskevicius et al., 2016, 2017; Karube et al., 2018; Reddy et al., 2017; Voropaeva et al., 2019; Bolen et al., 2020; Møller et al., 2000). It must be noted, though, that in some of these studies presenting no association, *TP53* mutations showed a non-significant tendency to lower PFS or OS or were associated with outcome in univariate analysis but not in the multivariate analysis. In addition, a combination of *TP53* mutations and deletions was also associated with unfavorable prognosis in two additional studies (Stefancikova et al., 2011; Schiefer et al., 2015), further supporting a possible prognostic value. Furthermore, given that different mutations were identified in different studies, discrepancies in results among studies suggest that different mutations in *TP53* could have different effects on DLBCL, as proposed above for other genes. In fact, mutations located in DNA binding domains have been suggested to have a higher effect on survival than mutations in other regions (Young et al., 2008, 2007; Karube et al., 2018), which would support this hypothesis.

Considering *DLBCL* subtypes separately, *TP53* was the unique gene with significant results studied by two or more studies, and it was associated with poor prognosis in GCB-DLBCL patients in 3/5 studies (Young et al., 2008; Zainuddin et al., 2009; Xu-Monette et al., 2012), whereas it showed no significant association in ABC or non-GC patients in 4/5 studies (Young et al., 2008, 2007; Zainuddin et al., 2009; Bolen et al., 2020); suggesting that, it could have a dual behavior depending on the DLBCL subtype, which could be explained by the different mechanisms underlying each subtype.

On the other hand, thirteen studies described significant associations between survival and somatic mutations or combinations of mutations and other alterations in multiple genes or specific pathways. In fact, taking into

account the heterogeneity observed in DLBCL, it seems unlikely that mutations in a single gene justify such variability, and an integrative analysis of the mutational status of different genes and pathways could improve the prognostic classification and the treatment choice.

Some studies combined pairs of genes or single pathways but, interestingly, a group of studies incorporated information about diverse genetic aberrations and other prognostic factors into prognostic models of DLBCL that could stratify patients into differentiated groups (Chapuy et al., 2018; Schmitz et al., 2018; Reddy et al., 2017; Bolen et al., 2020).

While most combinations have only been analyzed once, it is remarkable that some genes were included in several combinations. For instance, *TP53* was studied in combination with *CDKN2A*, methylation of *MIR34A* or within the p16INK4a/ARF-p53 pathway, the different combinations reflecting a negative effect on prognosis (Asmar et al., 2014; Karube et al., 2018; Grønbaek et al., 2000). *CREBBP* was also studied in combination with *EP300* and in different molecular subgroups, the combinations being associated with poorer prognosis. This is of note regarding that mutations in *CREBBP* alone have not been significantly associated with outcome, which supports the idea that combinations of mutations have a greater power to predict patients' outcome. On the other hand, while mutations in *NOTCH* pathway were associated with a worse outcome, in the different molecular subgroups mutations in *NOTCH1* are usually incorporated into the high risk groups while mutations in *NOTCH2* are included in groups of better prognosis, which suggests that mutations in different genes of the same pathway do not necessarily need to have the same effect.

Among the proposed prognostic models, Chapuy's classification was the one with the most robust evidence to be a useful tool, because it was first established that C3/C5 and C2 groups individually were significantly associated with worse outcome in comparison with C0/C1/C4 patients (Chapuy et al., 2018), and later their homologous G3 (enrichment of BCL2 and CREBBP) /G5 (enrichment of ABC subset) /G2 (enrichment of TP53 and REL) patients had worse outcome in comparison with G0/G1/G4 (Bolen et al., 2020). It is remarkable that G5 is characterized by enrichment of ABC subtype, which are generally related to worse outcome.

In conclusion, the incorporation of genetic alterations as prognosis markers into risk stratification systems could improve the classification of patients. However, further studies are required to validate the prognostic implication of the reported genetic alterations.

4.2. Genetic alterations as therapeutic targets

Nowadays, there is a wide range of available drugs that can target specific genes or pathways. Therefore, the introduction of drugs that target pathways of relevance in DLBCL could be of relevance in order to improve the outcome of the disease. In this context, we have identified eight articles proposing pairs of drugs and their target genes and alterations that could serve as new therapeutic strategies in DLBCL.

Among them, three combinations of mutated genes and targeted drugs were proposed by more than two studies: three studies proposed BCL2 inhibitors for *BCL2* mutants (Schiefer et al., 2015; Dubois et al., 2016; Ennishi et al., 2017), three studies proposed EZH2 inhibitors for *EZH2* mutants (Dubois et al., 2016; Karube et al., 2018; Dubois et al., 2015), and four studies proposed the BTK inhibitor ibrutinib for *MYD88* mutants (Dubois et al., 2016, 2017; Xu et al., 2017; Karube et al., 2018).

Regarding BCL inhibitors, BH3 mimetics was proposed as a possible therapeutic option for DLBCL patients. In fact, the BH3 domain of BCL2 was shown to be unaffected by the mutations detected in DLBCL patients (Dubois et al., 2016), indicating that BH3 mimetic activity would not be hampered. One of those BH3 mimetic drugs, venetoclax, was shown to have substantial antitumor activity in patients with B-cell lymphomas in a recently published study (Roberts et al., 2016).

On the other hand, phosphorylation of Bruton's tyrosine kinase (BTK) promotes nuclear factor kappa B (NF-κB) activity, which is a hallmark of ABC-DLBCL. Ibrutinib binds irreversibly to BTK and blocks its kinase activity. Consequently, it was hypothesized that ABC-DLBCL tumors, the viability of which depends on NF-KB activity, would respond to ibrutinib. Different studies have shown that, even though ABC DLBCL responds better to ibrutinib than GCB tumors regardless of the mutational landscape (Wilson et al., 2015), the presence of mutations in *MYD88* and/or *CD79B* increase its activity, while *CARD11* and *TNFAIP3* mutations impact negatively on its therapeutic activity (Fernández-Rodríguez et al., 2014; Dubois et al., 2016, 2017; Wilson et al., 2015). While CD79B and MYD88 are upstream of BTK in the NF-κB signaling pathway, CARD11 and TNFAIP3 are downstream effectors; thus, DLBCL with activating mutations in genes encoding for proteins with an effect downstream of BTK could escape the effect of its inhibitor, ibrutinib. Therefore, combinations of mutations in different genes should be considered before assigning a specific targeted therapy.

Recurrent somatic mutations inducing a gain-of-function of *EZH2* have been identified in DLBCL, and some cell lines with those mutations depend on EZH2's higher catalytic activity for proliferation (Dubois et al., 2015). Therefore, EZH2 inhibitors could lead to a blockade in uncontrolled proliferation when that kind of mutations are present in DLBCL, presenting an alternative therapeutic option. It must be noted that, depending on the specific mutations identified in *EZH2*, different drugs are available (Karube et al., 2018; Dubois et al., 2015; Italiano et al., 2018; Knutson et al., 2014, 2012).

Finally, in the last years more therapeutic opportunities have been described based on other genetic aberrations. For instance, drugs targeting B-cell receptor–dependent NF-KB activation (e.g., inhibitors of BTK and protein kinase C beta) for BN2 and MCD DLBCL subtypes; immune-checkpoint inhibitors for N1 subtype; or inhibitors of B-cell receptor proximal signaling (e.g., spleen tyrosine kinase [SYK] inhibitors) or the downstream PI3 kinase pathway for lesions that alter negative regulators of B-cell receptor signaling or the B-cell receptor subunits CD79A and CD79B (Schmitz et al., 2018).

4.3. Limitations

It must be noted that this review presented several limitations. First of all, the number of studies that analyzed some specific genes and combinations was limited and, therefore, reaching reliable conclusions was complicated, further data being necessary. Besides, the clinical and methodological heterogeneity among studies must be considered. Focusing on sample size heterogeneity, it varied from 30 (Ramis-Zaldivar et al., 2020) to 1001 patients (Reddy et al., 2017). Statistical significance is strongly influenced by the sample size, and an effect that fails to be significant at a specified alpha level in a small sample could be significant in larger samples. Therefore, the genes determined as non-prognosis biomarkers by studies with bigger samples are more reliable than those of smaller samples. In addition, it must be taken into account that the percentage of GCB/ABC subtype and IPI-group was different in each study (Table S1), and these differences could also influence divergence in prognosis. Moreover, the treatment schemas used also varied and the gene mutations pointed out as prognosis biomarkers, could really be predictive for only specific treatments. Furthermore, the included studies presented methodological heterogeneity in the way the mutations were analyzed and in the phenotypes analyzed, which could lead to differences in results. In addition, it is possible that some additional articles have been missed by our search strategy. Furthermore, there is a tendency to prioritize statistically significant results for publication, which may lead to a bias and an underrepresentation of non-significant results.

Looking into the future of the field, it must also be taken into consideration that, currently, most studies are centered in coding genes, which made these the focus of the present review. Remarkably, non-coding regions are gaining relevance as biomarkers in different cancer settings. Interestingly, as mentioned above, the combination of *MIR34A* methylation and *TP53* mutation was an independent factor for survival in DLBCL patients (Asmar et al., 2014) and miR34 mimics have been proposed as alternative therapeutic options in p53 deficient cancer cells

(Ji et al., 2008). Therefore, existing evidence suggests that a deep analysis of alterations in non-coding regions could further improve the establishment of biomarkers and therapeutic options in DLBCL.

5. Conclusions and future direction

DLBCL is a very complex disease and additional markers are needed for stratification of patients according to their prognosis and for the identification of novel therapeutic strategies. In this line, in this systematic review, we have deepened in the role of somatic mutations. Regarding their role as prognostic markers, most genes have been studied in a limited number of studies, further research being necessary to reach conclusions. Focusing on those genes that have been more extensively studied, mutations in *CD58* and *TP53* seem the most promising predictors of poor outcome. Remarkably, the combination of different alterations and other prognostic factors for the establishment of subtypes appears to be a powerful strategy. On the other hand, with the expansion of targeted therapeutics, more and more mutations are being described as targets or as predictors of response to specific drugs. Of note, EZH2 inhibitors have been proposed as candidate drug against mutated *EZH2* DLBCL and ibrutinib for DLBCL with mutations in *BCR*, *CD79B* and/or *MYD88* in different studies. We can conclude that this is a very promising field of study, which could help guide treatment choice in DLBCL yet further studies and clinical trials are needed.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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