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Next-generation prognostic assessment for diffuse large B-cell lymphoma

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Abstract

Current standard of care therapy for diffuse large B-cell lymphoma (DLBCL) cures a majority of patients with additional benefit in salvage therapy and autologous stem cell transplant for patients who relapse. The next generation of prognostic models for DLBCL aims to more accurately stratify patients for novel therapies and risk-adapted treatment strategies. This review discusses the significance of host genetic and tumor genomic alterations seen in DLBCL, clinical and epidemiologic factors, and how each can be integrated into risk stratification algorithms. In the future, treatment prediction and prognostic model development and subsequent validation will require data from a large number of DLBCL patients to establish sufficient statistical power to correctly predict outcome. Novel modeling approaches can augment these efforts.

Keywords

activated B cells; Cox regression models; diffuse large B-cell lymphoma; gene-expression profiling; logistic regression; molecular subtyping; risk prediction models

Diffuse large B-cell lymphoma (DLBCL) accounts for roughly a third of all non-Hodgkin lymphoma (NHL) cases diagnosed in the USA, comprising nearly 24,000 estimated new cases in 2015 [1]. DLBCL is an aggressive disease and for untreated patients median survival is typically less than a year [2]. However, with current first-line treatment regimens, DLBCL is often curable with more than 50% of patients alive and disease free at 5 years [3]. For fit, chemoresponsive patients with relapsed DLBCL, autologous stem cell transplantation (ASCT) has become the preferred salvage strategy. While a proportion of relapsing patients are not transplant eligible, ASCT can cure 30–50% of relapsed patients as compared with salvage chemotherapy without ASCT which cures less than 10% [4,5]. Despite these advances and clearly defined standard approaches for all patients, individuals with DLBCL have disparate outcomes based on varying demographic, clinical and

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biological factors. Herein, we review potential epidemiological, biological and clinical factors associated with DLBCL survival and examine existing and novel strategies for constructing prognostic models to stratify DLBCL patients into groups with different expected outcomes.

Potential implications of epidemiological risk factors as predictors of survival

The International Lymphoma Epidemiology Consortium (InterLymph) assembled the world's largest collection of individual patient-level data for NHL. InterLymph examined clinical, lifestyle and occupational variables [6] and performed a genome-wide association study [7] that identified epidemiological risk factors for the development of DLBCL. Some of these risk factors also are hypothesized to influence DLBCL survival. To date, the strongest known risk factor for DLBCL and other lymphomas is chronic immunosuppression, as seen in autoimmune diseases, hepatitis C infection or AIDS [8–10]. Other influential risk factors include genetics, comorbid conditions and environmental variables [11–13].

To identify genetic susceptibility loci for DLBCL, a team of InterLymph investigators performed a meta-analysis of genome-wide association study examining 3857 DLBCL cases and 7666 controls of European ancestry, with confirmatory genotyping in 1359 DLBCL patient samples and 4557 controls. Five single nucleotide variants (SNVs) in four loci achieved genome-wide significance: rs116446171 at 6p25.3 (a locus for *EXOC2*), rs2523607 *at* 6p21.33 (*HLA-B*), rs79480871 at 2p23.3 (*NCOA1*) and rs13255292 and rs4733601, at 8q24.21 (*PVT1*) [7]. While these findings identified relationships between these SNVs and genetic susceptibility to DLBCL, additional studies are needed to examine the relationships between these and other SNVs and DLBCL survival. The follow-up efforts of InterLymph continue to examine DLBCL survival data that could provide additional epidemiologic factors for risk stratification and use in prognostic models.

The best evidence for diet being a factor in DLBCL survival comes from associations with vitamin D deficiency among DLBCL patients. Vitamin D deficiency is common in the USA, and in a study 44% of patients with DLBCL had insufficient vitamin D levels within 4 months of diagnosis [14]. Drake *et al*. illustrated that patients with DLBCL and vitamin D deficiency had an inferior event-free survival (EFS) and overall survival (OS) [14]. A German study also found patients all treated with rituximab (R) had markedly different responses when separated by vitamin D levels less than 8 ng/ml and more than 8 ng/ml, yielding a 3-year EFS of 59 versus 79% and a 3-year OS of 70 versus 82%, respectively [15]. This study also found that vitamin D deficiency can impair R-mediated cellular cytotoxicity providing a mechanism for these differences in outcome. *In vitro* models showed that vitamin D replacement improves R-mediated cellular cytotoxicity, further suggesting that vitamin D replacement may enhance R efficacy and improve outcomes. These findings are based on a small retrospective trial and should be confirmed in a larger prospective study, which is currently ongoing.

Identifying high-risk biological subtypes of DLBCL by genetic & genomic subtyping

Approaches for classifying DLBCL by molecular subtype

Gene-expression profiling (GEP) and immunohistochemistry (IHC) have yielded at least three biologically distinct and prognostically meaningful molecular subgroups of DLBCL [16,17]: clustered with normal germinal center B cell (GCB); clustered with activated B cells (ABC); primary mediastinal B-cell lymphoma (PMBL). GEP remains a cornerstone in understanding the pathogenesis of DLBCL characterizing molecular subtypes that have distinct clinical behaviors and prognosis [18]. GEP defined subgroups have a significant prognostic value. In a study, the 5-year OS was 80% for GCB versus 45% for ABC [19]. An alternative approach to classifying DLBCL by GEP has been proposed by Shipp and colleagues that subdivides DLBCL by B-cell receptor signaling or host response subtypes [20,21]. Unfortunately, GEP using microarrays is not routinely performed in clinical practice, it is expensive and has been largely limited to academic institutions.

While IHC algorithms have been proposed as a more accessible option, IHC results do not reliably correlate with GEP analysis. A recent systematic review literature search and meta-analysis identified three clinical studies that included only GEP data, 18 that included just IHC data, and another three that used both to examine differences in outcome for GCB and ABC DLBCL patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [22]. This study found discordance in the results of IHC and GEP as prognostic tools, which may be due to technical variability that lowers accuracy of IHC classification for GCB and ABC [22,23]. Moreover, pooled results did not support the use of the Hans and Choi's IHC algorithms as means to predict OS or successfully stratify patients into distinct prognostic groups. Thus, GEP remains the preferred subtyping method for predicting DLBCL outcomes.

Most recently the Lymphoma/Leukemia Molecular Profiling Project's Lymph2Cx assay has shown great promise in bringing molecular subtyping into common practice [24]. It is a 20 gene assay – eight of which are overexpressed in ABC and seven are overexpressed in GCB, along with five housekeeping genes, which ensure the accurate replication of subtype assignment defined by Lenz *et al*. [16] Lymph2Cx is highly accurate, with >95% concordance. The assay has a 2% misassignment rate, which favorably compares with the 9, 6 and 17% rates of the Hans, Tally and Choi's IHC-based algorithms, respectively [25–27]. This method has been reported to have a turnaround time of less than 36 h, which would aid clinical trial selection and could guide medical practice. Future approaches to DLBCL management also can use these molecular signatures to isolate new therapeutic targets for high-risk disease or those DLBCL patients who relapse [12].

Germinal center B-cell-like DLBCL—GCB DLBCL gene expression looks similar to normal germinal center B cells [18], and 30–40% of GCBs have a translocation t(14;18), resulting in overexpression of the BCL2 oncoprotein [28]. Rituximab has substantially improved survival rates for GCB DLBCL [16]. With R-CHOP, the GCB subtype had a significantly better 3-year OS than the non-GCB subtype (85 vs 69%) [29].

Primary mediastinal DLBCL—In the 2008 WHO classification system, primary mediastinal (thymic) large B-cell lymphoma is classified as an entity distinct from DLBCL [30]. PMBL, an uncommon type of DLBCL, tends to occur as a bulky tumor in the anterior mediastinum in young females [17]. PMBL can rapidly progress causing local compression symptoms such as dysphagia and superior vena cava syndrome – perhaps resulting in more limited stage at time of diagnosis. PMBL is thought to arise from thymic B cells and has similar characteristic to Hodgkin lymphoma, with gain or amplification of 9p24 [31,32]. Activation of the NF-κB pathway is more frequently observed in the ABC and PMBL subtypes [33]. A Phase II retrospective study suggested dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-R-EPOCH) obviated the need for radiotherapy in patients with PMBL, with a complete response (CR) of 94% and EFS of 93% [34], which has been considered a meaningful clinical improvement when compared with standard R-CHOP that had a CR of 90% and EFS of 81% at nearly 3 years [35]. PMBL patients have excellent OS and a marked plateau in EFS [36, 37]. While the outcomes observed for patients who received DA-R-EPOCH without radiation are provocative; the results of a randomized trial are needed to address the role of radiation following completion of chemoimmunotherapy.

Activated B-cell-like DLBCL—ABC DLBCL – also classified within the non-germinal center B-cell (non-GCB) subtype based on some IHC algorithms – is associated with inferior survival rates when compared with other subtypes. ABC DLBCLs have recurrent trisomy 3 and constitutive activation of the NF-κB signaling pathway, which can prevent the apoptosis induced by chemotherapy [38]. ABC-specific mutations affect genes regulating NF-κB signaling, with TNFAIP3 (A20) and MYD88 being the most abundantly mutated. When compared with GCB DLBCL, patients with ABC DLBCL have a significantly worse outcome when treated with R-CHOP or DA-R-EPOCH-like chemotherapy [16, 28,39].

High-throughput sequencing & DLBCL molecular subtype

With the availability of high-throughput sequencing, studies emerged examining mutations and pathways involved in DLBCL pathogenesis. Whole genome and exome sequencing of lymphoma biopsy and unaffected matched normal tissue from the same patient have helped identify recurring gene mutations and specific pathways associated with DLBCL. Lohr *et al*. found mutations previously recognized in DLBCL: MYD88, CARD11, EZH2 and CREBBP and identified new mutations including: MEF2B, MLL2, BTG1, GNA13, ACTB, P2RY8, PCLO and TNFRSF14 [40]. Pasqualucci *et al*. integrated exome sequencing and genome-wide high-density SNV array analysis and identified CREBBP and EP300 mutations in DLBCL [41]. Morin *et al*. performed DNA and RNA sequencing and found somatic mutations in MLL2, a major tumor suppressor locus, and MEF2B – a histone modifying gene. Zhang *et al*. identified the recurrent mutations related to chromatin modification (ARID1A and MEF2B), NF-κB (CARD11 and TNFAIP3), PI3K (PIK3CD, PIK3R1 and MTOR), B-cell lineage (IRF8, POU2F2 and GNA13) and WNT signaling (WIF1) [42]. Together these analyses have identified genes that are expressed differentially in GCB and ABC DLBCL. Across these studies translocations of BCL2, MYC and mutations of EZH2 methyltransferase are more commonly seen in GCB DLBCL, while TMEM30A and

constitutive activation of the NF-κB transcription complex (with mutations of TNFAIP3, CARD11, CD79B and MYD88) are more common in ABC DLBCL.

Now that multiple genetic susceptibility loci and whole-exome sequencing data have been identified for DLBCL, these findings need to be appropriately incorporated into DLBCL prediction models. Large cohort studies should collect clinical data, known risk factors, genomics, GEP and survival data for DLBCL patients in order to build more accurate prognostic models. A large number of cases are necessary to create sufficient statistical power to identify the prognostic significance of these variables. Outcome prediction using these data can ultimately facilitate discussion between physicians and patients, enhance patient understanding and allow patients to make more educated decisions regarding their care.

Other biological subgroups

While molecular subtyping of DLBCL, based on 'cell-of-origin', has emerged as the primary approach for separating DLBCL by prognosis, other important biological subgroups have been defined. Double hit lymphoma (DHL) DLBCLs contain dual translocations involving both MYC and BCL2 or BCL6 [43] accounting for roughly 5% of the DLBCLs [44]. They are named 'double-hit' on the basis of their dual-genetic insults or 'triple-hit' lymphoma if all three re-arrangements coexist [45,46], resulting in a more aggressive clinical course and general poor response to standard therapy. Interestingly, greater than 90% of cases of MYC/BCL2 DHL are GCB subtype [44]. Patients with DHL currently have a poor OS, with a median survival of 13 versus 95 months for patients without DHL [44]. In one study, intense chemotherapy induction was associated with improved progression-free survival (PFS), but it had no effect on OS [47]. There was also no difference between patients who underwent ASCT in first remission and those who were observed during first CR. The dominant predictive factor for outcome that emerged was achievement of CR with induction therapy. A multivariable analysis found that age, performance status and extranodal disease, each lost prognostic significance, whereas advanced stage and LDH retained their importance for patients with DHL [47].

There are multiple other biomarkers discussed in current literature, with varying future prognostic significance [48–50]. Based on the expression of six genes, LMO2, BCL6 and FN1 were associated with longer survival while CCND2, SCYA3 and BCL2 were associated with shorter survival [51]. In multivariable model gene expression studies, LMO2 mRNA expression emerged as the strongest single predictor of superior outcome, improved OS and PFS in DLBCL patients [51,52]. This prognostic marker may assist in further understanding tumor pathogenesis and may facilitate the development of targeted therapeutic agents.

Other studies have characterized the role of miRNA in DLBCL. Expression of miR-18a, miR-181a and miR-222 are correlated with survival of patients treated with R-CHOP [53]. The association between miR-18a and shorter OS suggests that this miRNA predicts poor response to either upfront or salvage therapies. While expression of miR-181a and miR-222 shortens PFS, it does not impact OS. miR-18a predicts OS while miR-181a and miR-222

impact PFS; it can be inferred that the microRNAs have different biological effects on DLBCL cells. Further studies to elucidate their role in lymphomagenesis are required.

Standard treatments for DLBCL & their outcomes

The anthracycline chemotherapy regimen CHOP has been a part of the standard of care for DLBCL since the 1970's [54]. In 1997, the US FDA approved the CD20 monoclonal antibody, R, which to date has produced the most significant improvement in treatment and survival for DLBCL [12]. In 2002, randomized trial demonstrated that when R was added to standard regimen of CHOP, the 2-year OS increased from 57 to 70% [55]. Follow-up data from this study and other randomized controlled trials confirmed the benefits of R-CHOP, yielding a cure in nearly 60% of patients [3,56–60].

There have been many trials investigating potential successors to R-CHOP. A Phase III trial compared R-ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone and intrathecal methotrexate) to R-CHOP resulting in a superior 3-year EFS of 81 versus 67% and OS 92 versus 84% [61]. Unfortunately, R-ACVBP was associated with considerable toxicities. Other approaches have not improved OS beyond standard R-CHOP administered every 21 days [62–64] and R-CHOP remains the current standard therapy for nearly all patients with DLBCL. Despite initial response to chemoimmunotherapy, almost a third of patients have disease progression or relapse after first-line treatment [65].

The question of how to best manage relapsed patients was addressed by the landmark PARMA study comparing ASCT following two cycles of combination chemotherapy to conventional salvage therapy. EFS and OS were significantly improved with transplant (46 vs 12% and 53 vs 32%, respectively) [5]. Currently, the optimal pretransplant salvage regimen after R-CHOP failure remains debatable. The CORAL study randomly assigned patients in first relapse or who were refractory to first-line therapy to either salvage RICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, high-dose cytarabine and cisplatin). Following ASCT, the 3-year OS for RICE and R-DHAP were identical [4]. More importantly, this study showed the expected cure rates for DLBCL following ASCT in the modern chemoimmunotherapy era, were not as high as previously seen in the PARMA trial, meaning that more favorable risk patients were less likely to relapse following R-CHOP [4]. Relapse less than 12 months after completion of first-line therapy, and previous R exposure were shown to adversely affect the outcome in CORAL. In Europe, pixantrone is approved for the treatment of multiple relapsed DLBCL and serves as another alternative for this patient population [66]. At this time, there is no standard third-line therapy for patients with poor risk biological features. Novel therapeutic approaches continue to be examined.

Strategies to improve outcomes for ABC DLBCL

Novel agents such as bortezomib, ibrutinib and lenalidomide are agents approved for hematologic malignancies that hold promise to reduce adverse outcomes associated with ABC subtype DLBCL. Each of these agents has been integrated in clinical trials [67–70] after demonstrating selective activity in ABC DLBCL when added to RCHOP-based chemotherapy [71–75]. Therapies targeting the NF-κB pathway appear to be effective in

patients with ABC DLBCL [42,76]. Examples of such therapies include bortezomib (a proteasome inhibitor that weakly inhibits NF-κB activation), ibrutinib (an upstream B-cell receptor signaling pathway inhibitor) and lenalidomide (downregulating the transcription factors IRF4 and SPIB, then enhancing B-cell IFN-β production) [22,77]. Bortezomib alone has very limited activity in DLBCL, but when combined with DA-EPOCH chemotherapy in a Phase I trial, there was a significantly higher response (83 vs 13%) and median OS (10.8 vs 3.4 months) in ABC compared with GCB DLBCL [71]. Other Phase I trials paired bortezomib with R-CHOP, where no survival differences were observed between GCB and non-GCB, suggesting that this agent might improve outcomes for ABC DLBCL [78]. Bortezomib with standard R-CHOP results in 86% CR [78], compared with historical data of 75% for R-CHOP alone [55,58]. A randomized Phase II trial of R-CHOP versus bortezomib-R-CHOP has been completed and is awaiting data maturation.

As an oral Bruton's tyrosine kinase inhibitor, ibrutinib has shown single-drug activity in relapsed or refractory B-cell malignancies. A Phase II trial of ibrutinib in patients with relapsed DLBCL had a higher response rate in ABC (41%) when compared with GCB (5%) subgroup and OS of 9.7 months in ABC versus 3.4 months with GCB [79,80]. Ibrutinib has also been safely combined with R-CHOP [81] and this combination is now being compared with R-CHOP in a randomized trial. Lenalidomide is a novel agent with several mechanism of action including stimulation of the innate immune system, enhancing the antitumor activity of R and augmenting IFN-β and downregulating IRF4 in a cereblon-dependent fashion [82–84]. Lenalidomide used in combination with R-CHOP was given the name R2CHOP in Phase II studies, which yielded a response rate of 98%, with 80% achieving CR. With EFS and OS rates at 24 months, 59 and 78%, respectively. This finding has been successfully replicated in the REAL07 trial by Vitolo *et al*. in Italy [75]. There was no difference in 24 months PFS or OS for R2CHOP patients on the basis of non-GCB and GCB subtype [73,85], suggesting there is no longer an obvious difference in the outcome of patients with DLBCL. Validation of these finding is needed, and several Phase III randomized trials examining addition of a novel agent to R-CHOP are underway. Predictive and prognostic models are needed for each of these novel approaches to risk stratify patient and identify those who are most appropriate for each therapy. With the addition of novel treatment strategies, previously existing prognostic factors may lose their importance.

Clinical measures that predict DLBCL outcomes

Outcome prediction models continue to evolve with greater understanding of risk factors that influence DLBCL survival. The first, best-validated, and still most widely used tool is the international prognostic index (IPI), which was designed in 1993 to predict long-term outcomes for patients with DLBCL and other aggressive lymphomas. One point is assigned for stage III/IV disease, elevated LDH, age >60 years, ECOG >2 and involvement of >1 extranodal site. The original IPI system stratifies patients into four risk groups with a 5-year OS ranging from 26 to 73%. A notable weakness of this index is that it was developed prior to the integration of R into first-line chemoimmunotherapy [86]. While the IPI remains predictive, it does not adequately stratify DLBCL patients treated in a follow-up study during the R era [87]. In 2007, a revised IPI with three prognostic groups was introduced. Revised IPI redistributed the IPI factors to give a more clinically useful prediction of

outcome, identifying a very good (4-year OS: 94%), good (4-year OS: 79%) and poor (4-year OS: 55%) outcome, respectively [87].

Other prognostic models have been developed based on patients who received treatment during the R era. The National Comprehensive Cancer Network (NCCN)-IPI was created using cases treated with R. The NCCN-IPI was developed using traditional clinical factors. This NCCN-IPI model utilizes extra nodal locations such as lymphomatous involvement of major organs or the CNS as a more substantial predictor of aggressive disease than strictly the number of extra nodal sites. In the NCCN-IPI, age and the level of LDH above normal are weighted in a more balanced way than in the original IPI. While compared with the IPI, the NCCN-IPI better discriminates low- and high-risk subgroups (5-year OS: 96 vs 33%) than the IPI (5-year OS: 90 vs 54%), respectively [88].

A model focusing on the elderly – the E-IPI – (age cut-off 70 years rather than 60 years used in the IPI) provided better discrimination in outcome for older individuals treated with R-CHOP [89,90]. The E-IPI placed more people in the low-risk category and fewer in the high risk, than were previously assigned by IPI. The survival estimates among the reclassified patients showed a clear difference in the low and low-intermediate risk groups with a 3-year PFS of 28% and OS of 36% [89,90]. While many gene expression signatures and immunohistochemical markers are known (as described above), these are not yet included in comprehensive prognostic models. Novel approaches are needed that address the impact of R and incorporate these biological data.

Race has been shown to be a notable predictor of survival in more recent models. Distinct ethnicities, such as African–American, have a markedly worse outcome [91]. On average black patients with DLBCL in the USA present at a younger age, more advanced stage and have inferior survival statics when treated with the same regimen compared with their white counterparts [91,92]. In a study, the mean age of diagnosis for black patients was 51 years old compared with 68 years for white patients. In this analysis, 54% of black compared with 47% of white patients were presented with stage III/IV disease, and resulting 5-year survival rates were 38% for black versus 46% for white [92]. It can be inferred that race as a variable should be integrated into current models, or new prognostic model should be created accounting for the greater than a decade difference in median age of diagnosis and nearly ten-percentage points difference in 5-year survival. One retrospective cohort study suggested that the IPI model does not effectively stratify African–American DLBCL patients into groups with appropriately predicted OS [91].

Other clinical methods for stratifying patients

EFS24

The majority of patients respond to first-line R-CHOP, unfortunately 20–40% of patients either fail to achieve a first remission or they ultimately relapse. The average first relapse happens within 12–18 months of diagnosis – often with poor response to salvage therapy and stem cell transplant [4,93]. A study using data from the Mayo Clinic found that patients who remain event-free 2 years after diagnosis have excellent long-term outcomes with little lymphoma-related mortality by the 5-year follow-up [94]. These findings were successfully

replicated in an independent cohort from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). While an EFS of 24 months does not establish cure, only 8% of patients who were event-free at 24 months had a subsequent relapse. Clinical risk prediction models for achieving EFS24 could identify patients at high risk of early relapse, to help prioritize their need for alternative and more aggressive management.

PET/surveillance imaging

In 2007, the International Working Group Guidelines for lymphoma response incorporated fluorodeoxyglucose (FDG) PET-computed tomography (CT) into standard staging for FDG-avid lymphomas [95]. According to the current Lugano lymphoma assessment, PET-CT imaging has become a standard approach for the assessment of response in most lymphomas [96]. Imaging used for staging the lymphoma identifies disease location, defines disease extent, and offers prognostic information. To accomplish this, PET-CT provides a baseline to which scans at completion of therapy can be compared. These comparisons can determine response or disease progression.

Interim PET/CT (I-PET) use in DLBCL is currently under investigation, based on demonstrations of meaningful prognostic power in Hodgkin lymphoma [97, 98]. In current practice, I-PET is regularly ordered, yet the clinical utility of these scans remains unclear. A single I-PET scan does not differentiate chemoresistant lymphoma from CR and cannot be used to guide risk-adapted therapy. In a study, more than half of I-PET positive cases became PET-negative by the end of chemotherapy, and most of these slow responders had durable remissions [99]. I-PET in the R era has had a particularly poor predictive power. Rituximab can recruit inflammatory cells to sites of disease, and these inflammatory cells have a high rate of glucose metabolism making them FDG-avid, resulting in false-positive results on PET [97]. At present, a positive I-PET scan should not be used to intensify therapy, as this could place slow responders at risk for unnecessary treatment-related toxicity. Any positive I-PET or end-of-therapy PET requires biopsy confirmation of relapse prior to decision making regarding additional therapy.

The rationale for performing surveillance imaging is based on the assumption that if relapses are detected with lower tumor burden, then responses to second-line therapy will improve, which in turn will improve patients' OS. However, post-therapy surveillance imaging also has limited value for predicting relapse in DLBCL. The majority of DLBCL relapses are detected outside of planned follow-up, with 90% identified in response to patient-reported symptoms or abnormal physical exam or laboratory findings [100]. Improved early detection of relapse may result from better symptom education, with appropriate imaging to investigate concern [100,101]. Relapses detected solely via imaging have not been associated with superior survival in multiple studies, despite being detected at earlier stages [102]. The available data do not support the utility of routine surveillance imaging for follow-up of DLBCL or for use in predicting DLBCL outcomes.

Development of next-generation prognostic models for DLBCL

Several strategies and algorithms have been used to develop systems that predict the response and outcomes associated with a particular treatment strategy (predictive models)

and to stratify outcomes for individuals with a particular disease (prognostic models). Cox regression models and multivariable logistic regression (LR) have been the most commonly used approaches for developing prognostic models in medicine and have intuitive interpretations in the model structure [103]. For example, in the development of the IPI model, a multivariate Cox proportional hazard model identified five pretreatment features (age >60 years, stage III/IV disease, involvement of >1 extra nodal site, performance status ≥2 and elevated LDH) which were independently significant in predicting the OS, based on the training samples. Given that, the five significant risk factors had comparable relative risks; a simple approach to assess the total risks is to count the number of presenting risk factors (i.e., assigning one point for each presenting factor) and regroup into four categories (0–1, 2, 3 and 4–5 for low-, intermediate–low-, intermediate–high-, and high-risk groups, respectively). Model validation also showed that the IPI model was equally predictive in the validation of patient population.

One can also assign different scores for each risk factor based on its value to maximize the survival stratification across different risk subgroups. The stratification can be measured by the χ^2 statistics of the log rank test; a higher χ^2 value indicates larger difference in survival between the subgroups. In a more general case, one can define a risk formula based on the fitted Cox model. For any patient, his risk score can be calculated from the formula and this formula can be used to determine the risk group based on the preset cut-off values of risk scores. The cut-off values are selected to achieve the optimal survival stratifications in a desirable prognostic model. These approaches have been previously used in developing other prognostic models in the literature, such as for the mantle cell lymphoma IPI [104].

In addition to traditional survival analysis and score-based prognostic models, many novel approaches developed in the machine learning community can be utilized for cancer prediction and prognosis [105–107]. Examples include artificial neural network, support vector machine, Bayesian network and random forest models [108]. These new models can allow more flexible structure, which can help identify critical underlying patterns from complex, high-volume or perhaps noisy dataset.

Clinical prognostic models are commonly developed using commonly recorded patient demographic and pretreatment clinical variables including the age categories, sex, Ann Arbor stage and presence of B symptoms, number of nodal and extranodal sites involved, performance status and laboratory values. A common output for prognostic models has been the predicted probability that a patient would survive to a specific landmark (such as at least 5 years). The 5-year landmark is meaningful because this is the time period when patients with DLBCL can be considered cured [2–3,56,58,91,109–110]. Novel prognostic models for DLBCL can also utilize molecular characteristics of DLBCL such as ABC, GCB, PMBL and DHL subtype as well as genomic markers such as MYD88. Construction of such models using traditional approaches will require a large comprehensive clinical data consisting of all these variables for each individual patient to construct adequate testing and training datasets, which could be a challenging requirement as novel prognostic factors were oftentimes identified from separate studies with separate datasets. Beyond the series of existing prognostic models for specific subgroups of DLBCL patients, some investigators are interested in developing a unified model considering the effects of the prognostic factors that

have been well defined so far. Below, we describe a multilevel model framework to integrate the emerging data from published studies along with the individual-level data available from public datasets.

Level 1: basic model based on public population data

In the initial phase, a basic survival model for the general DLBCL population can be constructed, which can capture the background mortality and cause-specific (lymphoma-related) mortality. Cause-specific survival in a baseline parametric form can be estimated from public use individual-level datasets such as the Surveillance Epidemiology and End Results (SEER) data. Many investigators have considerable experience with manipulating and performing analyses with SEER data for patients with lymphoma [111–119] and have previously used SEER data to construct models of cancer outcomes [120–122] and to examine risk prediction for DLBCL [123]. Survival analysis techniques [124] and natural history microsimulation [125, 126] can be combined for such model development.

Level 2: extended modeling based on published data from clinical studies of biomarkers & treatments

In addition to the individual patient-level data, emerging evidence regarding outcomes stratified by various treatment or biological factors from published studies are valuable sources to enrich a DLBCL disease model. Typically one cannot obtain the patient-level data used in each clinical study. However, an investigator can sample the values of the factors based on the summary of patient characteristics in the published paper, feed the values of the variables that have been previously calibrated and calibrate the effect (i.e., relative risks and hazard ratios, among others) of new factors by comparing the simulated OS and the survival curve presented in the published paper. Modeling studies have used this approach to simulate and compare outcomes for cancer treatments [122,127–128]. For example, a second-level DLBCL prognostic model might expand on the basic model by incorporating new factors from published studies of:

- The standard of care treatment: R-CHOP in Phase III clinical trials [3,56–60,62–64];
- Biological subtypes of DLBCL [16,18,22,25– 26,28,129–133];
- Novel treatments such as emerging studies for lenalidomide + R-CHOP, ibrutinib + R-CHOP, obinutuzumab + CHOP, bortezomib + R-CHOP, carfilzomib + R-CHOP [71–75,134];
- Treatment-specific biological effects such as outcomes for non-GCB DLBCL in the Phase II study of lenalidomide + R-CHOP [73].

Comprehensive model validation & use

Just as in traditional prediction and prognostic model construction, each step of model development should validate the model after model training (i.e., calibrating the effect of each risk factor), using approaches such as using tenfold cross validation and bootstrapping to measure the accuracy of model prediction in the unseen dataset [123].

The primary performance measure for survival prediction models is model calibration, which can be assessed using measures such as the Hosmer-Lemeshow (H–L) goodness-of-fit test [103]. The H-L statistic measures the differences between the expected and predicted outcomes in subgroups of the population. The H-L test for goodness-of-fit for the prediction models assesses whether or not the observed event rates (e.g., 10-year OS) match expected event rates in subgroups of the model population. Model calibration also can be visualized using a calibration curve plot, in which the 45-degree line represents the perfect calibration and the points to the left (or right) represent underestimations (or overestimations) of risk. Model discrimination can be assessed by plotting the receiver-operator characteristics curve [135] based on comparing the observed and predicted survival for test cases and calculating the AUC (also known as the c-statistic) and using the two-tailed DeLong method [136] to compare the AUCs for different models.

Once a validated prediction model is constructed, for any given values of patient prognostic/predictive factors, the model can generate the survival curves or point estimates of survival (e.g., 1-, 2- or 5-year OS) as well as the corresponding CIs. Then, the estimated results for every possible combination of input factors can be implemented in a prognosis assessment tool (similar to an existing online interactive tool for breast cancer) [137]. Using such a tool, health professionals and patients can choose the input value of each factor, and then obtain the estimates of survival. The proposed modeling approach incorporates population-based data to account for the fact that patients who are participants in clinical studies may not be representative of the average patient who presents in daily practice.

Conclusion & future perspective

The next generation of prognostic models will more accurately stratify patients for novel or risk-adapted therapies [40]. These prognostic models can be modified to incorporate individual patient-level information, and survival curves from published data regarding the activated pathways and targets present in their specific tumor. They will incorporate PET scan findings, other imaging results and pertinent sequencing data in conjunction with traditional clinical factors from the IPI index. New models may assign varying weight to new factors. Other distinguishing factors that could be calibrated into a prediction model are fast/slow metabolic response and GCB/ABC subclassifications. These differences need to be appropriately reflected in the risk stratification and proposed as a means to tailor therapeutic strategies [138].

Although many patients with DLBCL are cured, unfortunately up to 40% will die of the disease [40]. Second-line treatment strategies improve outcome by additional high-dose standard chemotherapy regimens, with the goal of getting responders to auto-stem cell transplant [139,140]. More encompassing prognostic models may identify poor-risk patients earlier, allowing clinicians to choose an appropriate treatment regimen upfront. Further research also is necessary to explore the influences, risk management strategies and treatment preferences of DLBCL patients in order to incorporate novel decision-making tools into a clinical practice.

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EXECUTIVE SUMMARY

Background

- Diffuse large B-cell lymphoma (DLBC) accounts for roughly a third of all non-Hodgkin lymphoma.
- Current first-line treatment regimens for DLBCL have a disease-free 5 years survival of more than 50%.
- Autologous stem cell transplantation (ASCT) can cure 30–50% of relapsed patients, compared with salvage chemotherapy which alone cures less than 10%.

Epidemiological risk factors as predictors of survival

- The strongest known risk factor for DLBCL is chronic immunosuppression, but its impact on survival is less clear.
- Vitamin D deficiency is a dietary factor that appears to be influence survival for patients with DLBCL.

High-risk biological subtypes of DLBCL

- Gene expression profiling and immunohistochemistry have yielded at least three molecular subgroups of DLBCL.
- For DLBCL patients treated with standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), those with the germinal center B-cell (GCB) subtype had significantly better survival than patients with the activated B-cell (ABC) subtype.
- Novel gene-expression profiling approaches may allow molecular subtyping to become a part of common practice, produce accurate identification of ABC and GCB subtype and provide better distinction of prognostic risk groups than immunohistochemistry methods.
- Double hit and triple hit DLBCL are other subgroups associated with worse survival.

Standard treatments for DLBCL & their outcomes

- R-CHOP cures nearly 60% of DLBCL patients.

Strategies to improve outcomes for ABC DLBCL

- Novel agents such as bortezomib, ibrutinib and lenalidomide have been integrated into R-CHOP in clinical trials, increasing the complete response and lengthening the overall survival in ABC DLBCL in Phase I and II trials.

Clinical measures that predict DLBCL outcomes

- The first and most commonly used DLBCL prognostic model is the international prognostic index (IPI), created prior to common use of R-CHOP, the current standard of care.

- Race and age have been shown to be notable predictors of survival. African–Americans have markedly worse outcome in population-based studies; however, race is not yet integrated into most prognostic models.

Development of next-generation prognostic models for DLBCL

- Cox regression models and multivariable logistic regression are commonly used to develop prognostic models in medicine.
- A basic survival model for DLBCL can be constructed to capture the background mortality and cause-specific (lymphoma-related) mortality.
- Each step of prognostic model construction requires training and validation and a means to measure the accuracy of model prediction.

Future perspective

- The next generation of prognostic models will more accurately stratify patients for novel and risk-adapted therapies.
- Future models need to incorporate PET scan findings, pertinent sequencing data, GCB/ABC subclassifications, along with traditional clinical factors from the IPI index.