Modern, real-world patterns of care and clinical outcomes among patients with newly diagnosed diffuse large B-cell lymphoma with or without double/triple-hit status in the United States

Patients with diffuse large B-cell lymphoma (DLBCL) and double-hit or triple-hit cytogenetics (DHL/THL) historically had a poor prognosis when treated with the standard front-line regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[1,2] Patterns of care and subsequent clinical outcomes of patients with DHL/THL had been largely determined from multiple retrospective studies, most without any direct comparisons to patients without DHL/THL. A single-arm, phase II study utilizing dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (R-EPOCH) in 24 patients with DHL/THL showed a 4-year event-free survival of 73%, which was significantly higher than that of historical controls.[3] These data led to the adoption of dose-adjusted R-EPOCH as the preferred treatment for DHL/THL. A recent phase III study comparing R-CHOP *versus* dose-adjusted R-EPOCH included a small cohort of patients with DHL/THL, which precluded a comparison of efficacy.[10]

In this study, we aimed to evaluate the patterns of care and clinical outcomes of DLBCL from 2011 to the present day among a contemporary cohort of patients with newly diagnosed DLBCL. We also compared the outcomes of patients with DHL/THL DLBCL morphology treated with R-CHOP and R-EPOCH regimens in this population.

This retrospective, observational study utilized the nationwide Flatiron Health electronic health record-derived database. This is a longitudinal database containing de-identified patient-level data, curated via a combination of tech-enabled search engines and abstractors.[4] During the study period, data originated from approximately 280 US cancer clinics (~800 sites of care). We included adult patients (>18 years at diagnosis) with a confirmed diagnosis of the following histological subtypes of lymphoma: DLBCL not otherwise specified, DHL, Epstein-Barr virus-positive DLBCL, and T-cell/histiocyte-rich large B-cell lymphoma. We included patients diagnosed on or after January 1, 2011 who had at least two electronic health record-documented visits on or after that date, with at least 6 months of potential follow-up (diagnosis prior to January 31, 2021).

Cytogenetic testing groups were defined by the documentation of cytogenetic test results based on fluorescence *in situ* hybridization (FISH) studies and/or karyotyping before or up to 6 weeks after initiation of first-line treatment. Patients were categorized into three groups: documented DHL/THL, documented testing but negative for DHL/THL (not DHL/THL), and no documented FISH/karyotype testing results (no documented testing for *MYC*).

The primary outcome measure was real-world overall survival (OS), defined as time from initiation of first-line treatment to date of death or censoring at last confirmed activity.[5] The secondary outcome was time to next treatment (TTNT) as a proxy for progression-free survival, defined as time from initiation of first-line treatment to second-line treatment, or date of death (whichever came first), or censoring at last confirmed activity. Adjusted covariates included age, sex, race/ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status at first-line treatment initiation, elevated lactate dehydrogenase and more than one site of extranodal disease. ECOG performance status was based on the value reported within 30 days prior to and 7 days after initiation of first-line treatment.

We used the Kaplan-Meier method and log-rank tests to estimate real-world OS and TTNT by cytogenetic testing group among all eligible patients with DLBCL. Among patients with DHL/THL who received R-CHOP or R-EPOCH as first-line treatment, the Kaplan-Meier method was used to estimate median real-world OS and TTNT. Multivariable Cox proportional hazards models were used to assess the impact of first-line treatment group (R-CHOP *vs.* R-EPOCH) on real-world OS and TTNT, adjusting for age, sex, race, ECOG performance status, stage, year of diagnosis, extranodal disease status and elevated lactate dehydrogenase levels. Statistical analyses were conducted using RStudio 3.6.1 software.

We included 6,412 patients with DLBCL in our total cohort (Table 1, *Online Supplementary Figure S1A*), with a mix of patients being cared for in the community (87%) and academic settings (13%). Among them, 2,604 (40.6%) patients did not have any documented cytogenetic testing before or up to 6 weeks after initiation of first-line treatment. Among patients with documented cytogenetic testing, 304 (8%) had DHL/THL and 3,504 (92%) patients did not (Table 1). Among the cases of DHL/THL, there were 176 (57.9%) patients with *MYC/BCL2*, 57 (18.8%) patients with *MYC/BCL6*, and 71 (23.4%) patients with *MYC/BCL2/BCL6*

Table 1. Baseline characteristics by cytogenetic testing groups.

Baseline characteristics	All N=6,412	No documented tests N=2,604	Not DHL/THL N=3,504	DHL/THL N=304	*P* overall
Age at diagnosis, N (%)					<0.001
≤40 years	279 (4.4)	86 (3.3)	181 (5.2)	12 (3.9)	
41-60 years	1,490 (23.2)	573 (22.0)	834 (23.8)	83 (27.3)	
61-75 years	2,870 (44.8)	1,145 (44)	1,594 (45.5)	131 (43.1)	
>75 years	1,773 (27.7)	800 (30.7)	895 (25.5)	78 (25.7)	
Sex, N (%)					0.004
Female	2,796 (43.6)	1,200 (46.1)	1,466 (41.8)	130 (42.8)	
Male	3,615 (56.4)	1,403 (53.9)	2,038 (58.2)	174 (57.2)	
Race/ethnicity, N (%)					0.042
Non-Hispanic white	4,307 (67.2)	1,791 (68.8)	2,313 (66.0)	203 (66.8)	
Non-Hispanic black	378 (5.9)	150 (5.8)	215 (6.1)	13 (4.3)	
Hispanic or Latino	402 (6.3)	167 (6.4)	216 (6.2)	19 (6.2)	
Asian	140 (2.2)	42 (1.6)	94 (2.7)	4 (1.3)	
Other/unknown	1,185 (18.5)	454 (17.4)	666 (19.0)	65 (21.4)	
ECOG PS at initiation of first-line therapy, N (%)					<0.001
0	1,528 (23.8)	496 (19.0)	945 (27.0)	87 (28.6)	
1	1,451 (22.6)	515 (19.8)	870 (24.8)	66 (21.7)	
≥2	681 (10.6)	282 (10.8)	360 (10.3)	39 (12.8)	
Unknown	2,752 (42.9)	1,311 (50.3)	1,329 (37.9)	112 (36.8)	
Cell of origin, N (%)					<0.001
Germinal B cell	2,096 (32.7)	660 (25.3)	1,267 (36.2)	169 (55.6)	
Non-germinal B cell/activated B cell	1,433 (22.3)	455 (17.5)	949 (27.1)	29 (9.5)	
Unknown/not documented	2,883 (45.0)	1,489 (57.2)	1,288 (36.8)	106 (34.9)	
Stage at diagnosis, N (%)					<0.001
I-II	1,762 (27.5)	717 (27.5)	996 (28.4)	49 (16.1)	
III-IV	3,283 (51.2)	1,247 (47.9)	1,854 (52.9)	182 (59.9)	
Unknown	1,367 (21.3)	640 (24.6)	654 (18.7)	73 (24.0)	
B symptoms, N (%)					<0.001
Other/unknown B symptoms	834 (13.0)	417 (16.0)	384 (11.0)	33 (10.9)	
With B symptoms	2,325 (36.3)	894 (34.3)	1,317 (37.6)	114 (37.5)	
Without B symptoms	3,253 (50.7)	1,293 (49.7)	1,803 (51.5)	157 (51.6)	
≥1 Extra nodal site, N (%)					0.300
Yes	3,527 (55.0)	1,405 (54.0)	1,947 (55.6)	175 (57.6)	
No/unknown	2,885 (45.0)	1,199 (46.0)	1,557 (44.4)	129 (42.4)	
Transformation, N (%)					0.001
Yes	1,104 (17.2)	450 (17.3)	578 (16.5)	76 (25.0)	
No/unknown	5,308 (82.8)	2,154 (82.7)	2,926 (83.5)	228 (75.0)	
LDH ratio at initiation of first-line treatment, N (%)					<0.001
Normal	1,846 (28.8)	678 (26.0)	1,106 (31.6)	62 (20.4)	
Elevated, up to 3xULN	1,500 (23.4)	505 (19.4)	902 (25.7)	93 (30.6)	
>3x ULN	226 (3.5)	82 (3.1)	114 (3.3)	30 (9.9)	
Unknown	2,840 (44.3)	1,339 (51.4)	1,382 (39.4)	119 (39.1)	
Duration from diagnosis to initiation of first-line treatment, N (%)					<0.001
≤14 days	2,210 (34.5)	958 (36.8)	1,126 (32.1)	126 (41.4)	
>14 days	4,202 (65.5)	1,646 (63.2)	2,378 (67.9)	178 (58.6)	
First-line treatment, N (%)					<0.001
R-CHOP	4,643 (72.4)	1,917 (73.6)	2,629 (75)	97 (31.9)	
R-EPOCH	456 (7.1)	92 (3.5)	233 (6.6)	131 (43.1)	
Other	1,313 (20.5)	595 (22.8)	642 (18.3)	76 (25.0)	

DHL: double-hit lymphoma; THL: triple-hit lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin.

(THL) rearrangements. The annual rates of documented cytogenetic testing increased consistently over the last decade, from 37% in 2011 to 82% in 2021 (*Online Supplementary Figure S1B*).

Among patients with documented cytogenetic test results, patients with DHL/THL were more likely to be younger, have a germinal center B-cell subtype, stage III-IV disease, transformed lymphoma, elevated lactate dehydrogenase, and to have started first-line treatment within 14 days of diagnosis, when compared to patients without DHL/THL. Among patients with DHL/THL, those who received R-CHOP as first-line treatment were more likely to be older and have THL, compared with patients who received R-EPOCH. Other baseline characteristics were similar between the two treatment groups.

R-CHOP was the most common first-line treatment overall, but the proportion of patients who received first-line R-CHOP was much lower in the DHL/THL cohort (29%) than in the group of patients who did not have DHL/THL (69%) or did not have documented test results (70%) (*Online Supplementary Figure S2*). Patients with DHL/THL were more likely to receive R-EPOCH as first-line treatment (43%) than were patients who did not have DHL/THL (4.7%). Choices for second- and third-line treatments varied widely between all groups; second-line therapy was received by 38% of patients with DHL/THL, by 27% without DHL/THL, and by 28% of patients without documentation of cytogenetic testing (*Online Supplementary Figure S2*). The proportion of patients who received second-line therapy or underwent transplantation was higher among patients with DHL/THL than among those without DHL/THL.

The median duration of follow-up for the entire cohort was

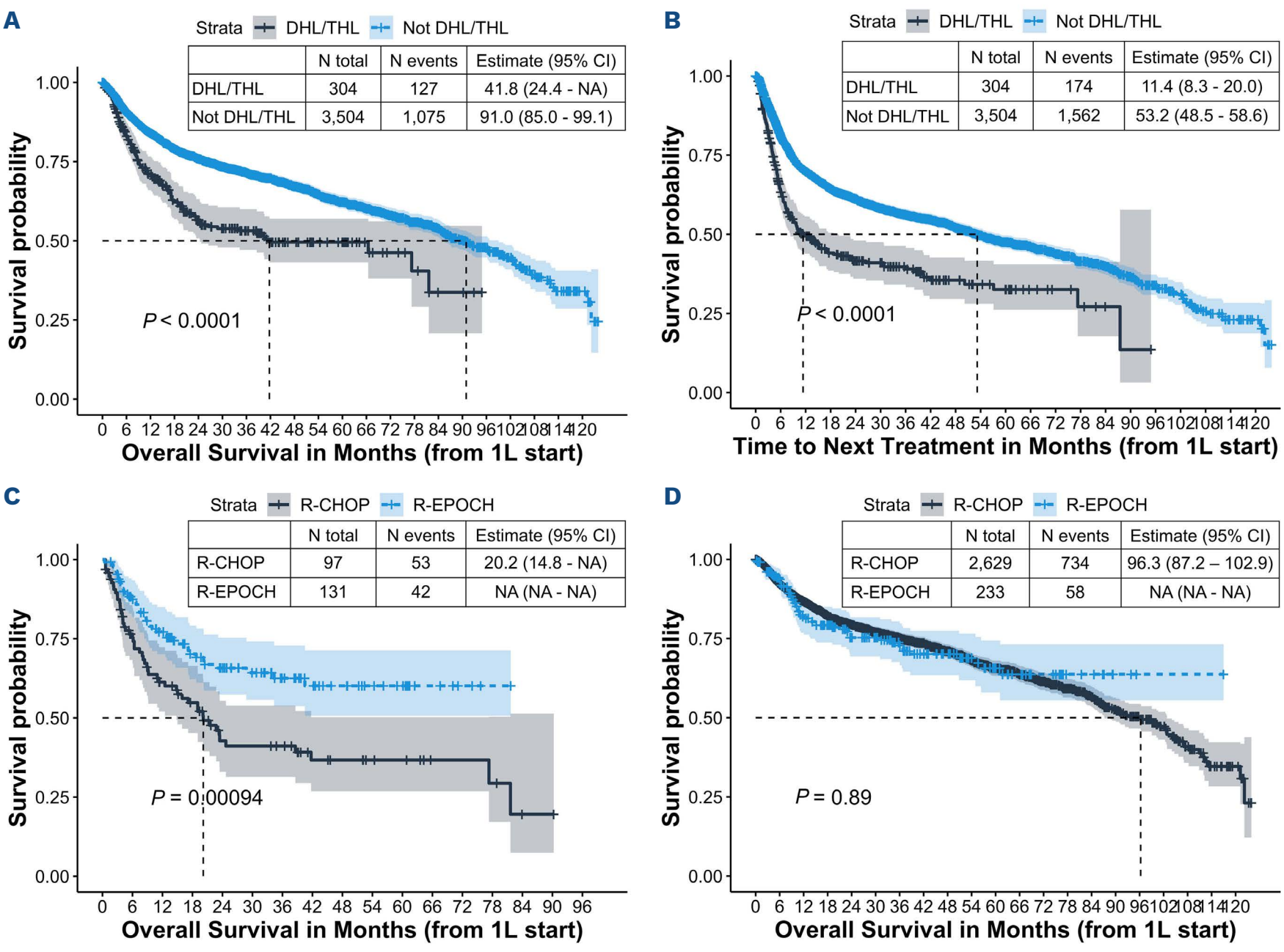
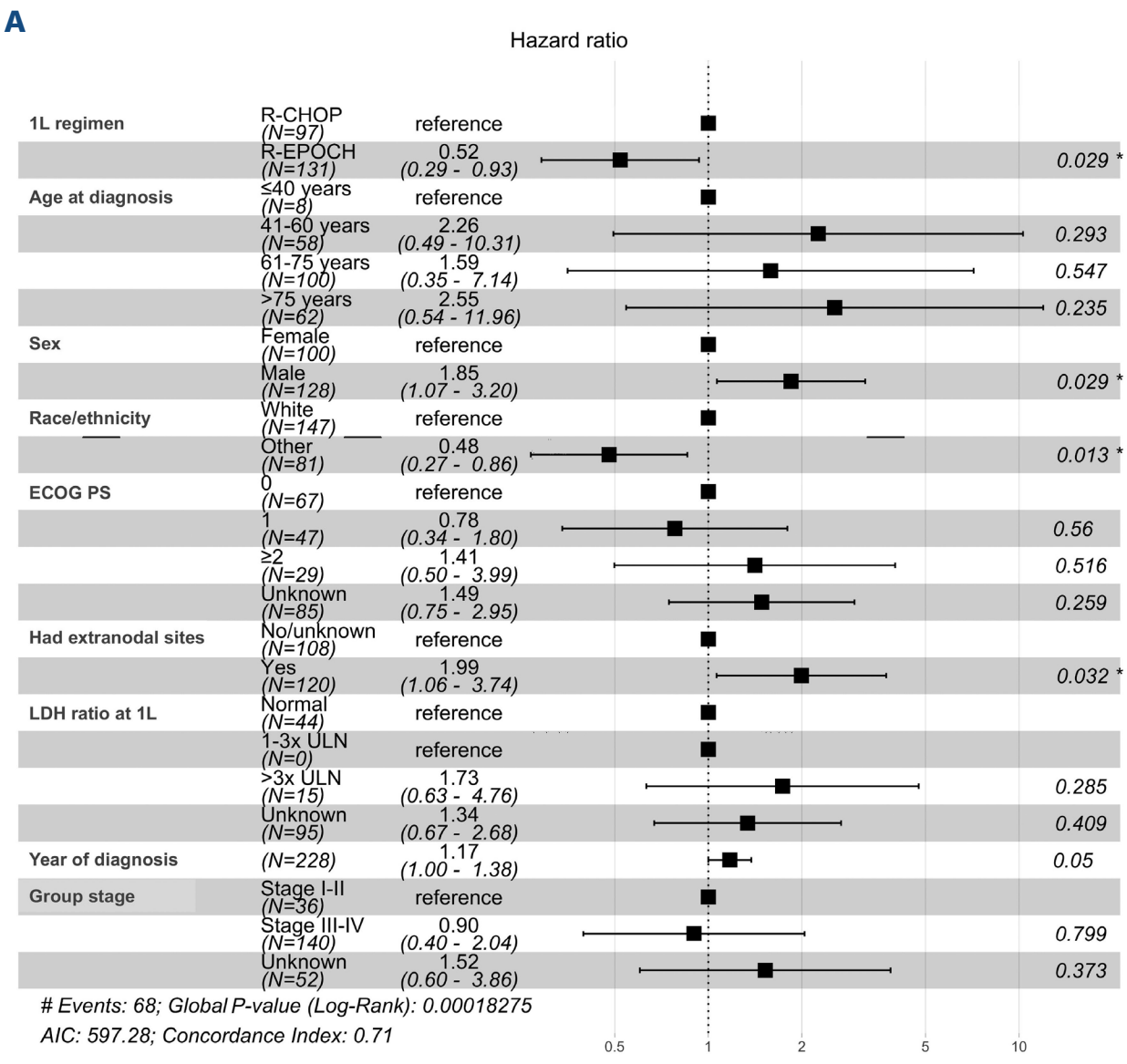


Figure 1. Kaplan-Meier curves of overall survival. (A, B) Real-world overall survival (A) and time to next treatment (B) stratified by gene-rearrangement status among patients who had undergone cytogenetic testing. (C, D) Real-world overall survival stratified by first-line treatment (R-CHOP *vs.* R-EPOCH) among patients with diffuse large B-cell lymphoma divided by cytogenetic group into those with double/triple hit lymphoma (C) and those without double/triple hit lymphoma (D). DHL: double-hit lymphoma; THL: triple-hit lymphoma; 95% CI: 95% confidence interval; 1L; first-line treatment; NA: not available; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin.



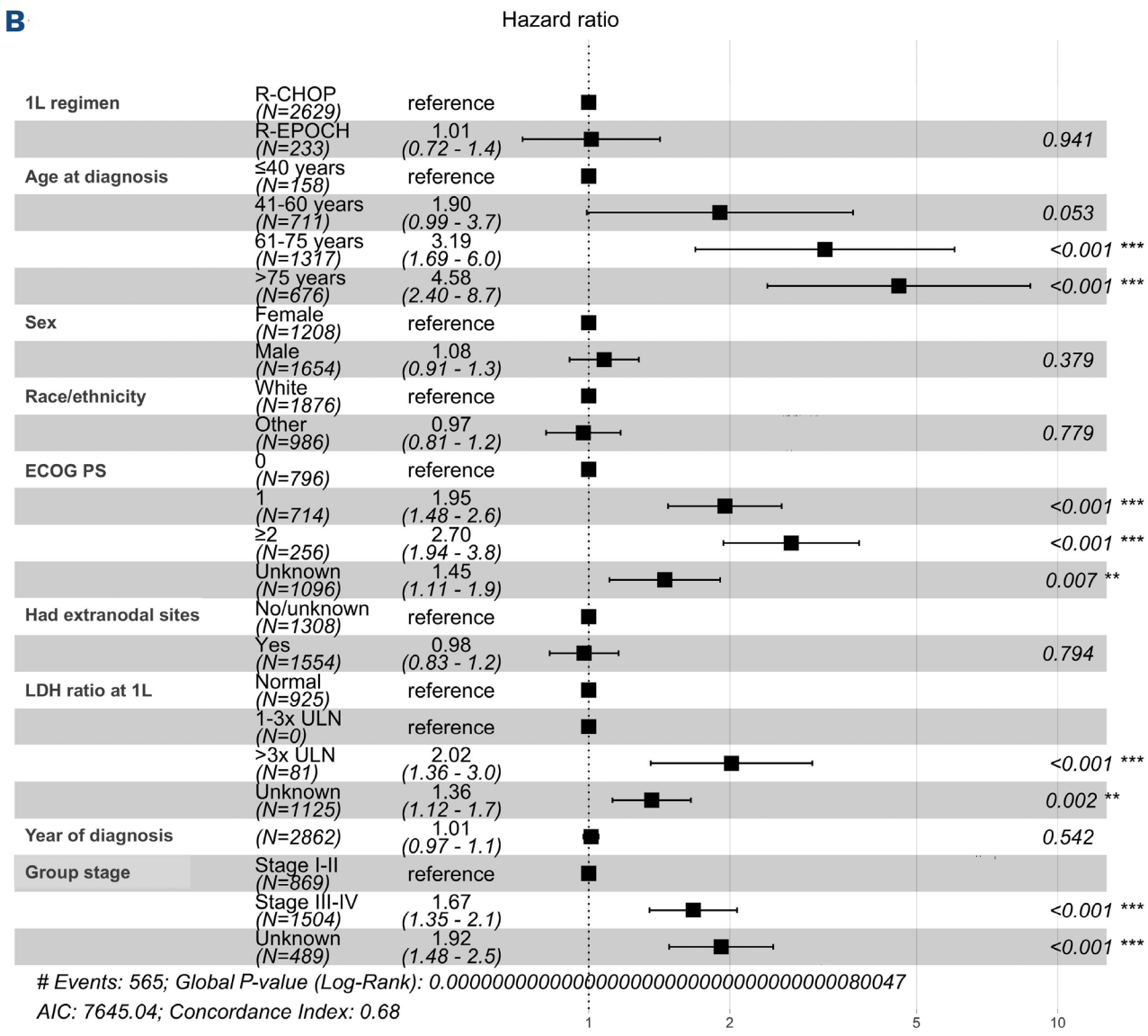


Figure 2. Multivariable analysis among cytogenetic testing groups. (A, B) Adjusted hazard ratios for real-world overall survival by first-line treatment among patients with diffuse large B-cell lymphoma documented as having double/triple-hit lymphoma (A) or not having double/triple hit lymphoma (B). 1L: first-line treatment; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; AIC: Akaike information criterion.

27.5 months (interquartile range, 10.2-56.3). Among all the patients, those with DHL/THL had worse real-world OS from initiation of first-line treatment (median: 41.7 months; 95% confidence interval [95% CI]: 24.4-not available [NA]), compared with patients who did not have DHL/THL (median: 91.0 months; 95% CI: 85.0-99.1) and patients without documented cytogenetic tests (median: 88.1 months; 95% CI: 83.3-95.0) (P<0.001) (Figure 1A and *data not shown*). Similar patterns were observed for TTNT; patients with DHL/THL had a shorter median TTNT from first-line treatment initiation (11.4 months; 95% CI: 8.3-20.0), compared with patients who did not have DHL/THL (53.2 months; 95% CI: 48.5-58.6) and patients without documented cytogenetic tests (50.7 months; 95% CI: 45.7-57.3) (P<0.001) (Figure 1B).

Among patients with DHL/THL who received R-CHOP (n=97) or R-EPOCH (n=131) as first-line treatment, patients receiving R-EPOCH had significantly longer real-world OS (median: not reached) compared with patients receiving R-CHOP (median: 20 months; 95% CI: 14.8-NA; P=0.001) (Figure 1C). Among patients who did not have DHL/THL, there was no difference in real-world OS between patients treated with R-CHOP or R-EPOCH (Figure 1D).

After adjusting for demographic and clinical characteristics among patients with DHL/THL, those who received R-EPOCH had a 50% lower risk of death (adjusted hazard ratio: 0.50; 95% CI: 0.33-0.77) than that of patients receiving R-CHOP as first-line treatment (Figure 2). Patients with an ECOG performance status greater than 2 (n=29) and male patients (n=128) also had higher hazard ratios for death. Additional sensitivity analysis adjusting for time to treatment initiation, or excluding patients who received methotrexate, patients undergoing transplant in first-line, those aged ≥80 years, those with transformed DLBCL, and patients who switched therapies within 18 weeks of starting first-line treatment did not change the results materially (*Online Supplementary Table S1*). We also conducted multiple imputation analysis when data were missing in >10% cases as well as inverse probability of treatment weighting analysis; however, the association of improved OS with R-EPOCH among DHL/THL persisted.

To the best of our knowledge, this is the largest direct comparison of the outcomes of DLBCL with and without DHL/THL among more than 6,000 patients in the real-world setting. With rapidly evolving standards of care in DLBCL in terms of cytogenetic testing and treatments, this study gives us the most recent assessment of survival outcomes. Although we found that 40% of newly diagnosed DLBCL cases in the entire period of our study did not have documented cytogenetic test results, we noted that testing rates increased steadily over time, with almost 80% of cases having documented testing in 2021.

Our study was able to compare outcomes between the two commonly used regimens, R-CHOP and R-EPOCH, in newly diagnosed DHL/THL with DLBCL morphology. Prior studies showed an improved progression-free survival, but not OS, with the use of R-EPOCH compared with R-CHOP in DHL/THL.[2,6] In a real-world setting we found that patients treated with R-EPOCH had a longer median OS compared with those treated with R-CHOP, even after adjusting for demographic and clinical factors. Furthermore, the longer duration of OS in our study compared with older studies for DHL/THL suggests an improvement in therapies over the last decade.

The biggest strength of our study is the large number of diverse USA oncology practices and patients involved, which allowed a pragmatic assessment of outcomes in the real-world setting.[4] Furthermore, our source data provided granularity of clinical variables at the patient level, enabling more robust outcome analyses across several sub-cohorts of interest than possible from prior single-center or pooled analyses, and we used a real-world composite mortality endpoint with high reliability.[5]

However, our study also has limitations and potential for biases. We mitigated for potential immortal time bias in testing by limiting our inclusion criteria to a testing window at diagnosis. Missing data was another limitation, but we conducted sensitivity analysis using multiple imputation which did not change results significantly. Although we controlled for several known prognostic variables in a multivariate approach, we were unable to account for additional factors that may contribute to the choice of treatments such as patient/physician preference, comorbidities, and overall health status. Additionally, we did not have data on the specific *MYC* translocation partner (IgH or non-IgH), which precluded assessment of its impact on prognosis, as shown before.[7]

In summary, our data showed, in a real-world setting, that R-EPOCH was associated with better OS compared with R-CHOP among patients with DHL/THL, and no difference among patients without DHL/THL. Our study also suggests that cytogenetic assessment may be an imperfect prognostic tool, with 5-year survival rates among DHL/THL cases of over 60% in the R-EPOCH group and 30% in the R-CHOP cohort. In the last 5 years, novel prognostic categories beyond cell of origin and DHL/THL status have been defined using next-generation sequencing,[27-29] and may offer better opportunities for designing future prospective trials as well as real-world studies.

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Contributions

GG and ES conceived and designed the study; GG, TM, WW, JR and ES analyzed and interpreted the data; all authors were involved in writing the manuscript, gave their final approval of the submitted version and are accountable for all aspects of the work.

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Data-sharing statement

The data that support the findings of this study originated from Flatiron Health, Inc. The de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

References

1. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of patients with double-hit lymphoma who achieve first complete remission. J Clin Oncol. 2017;35(20):2260-2267.
2. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354-2361.
3. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609-e617.
4. Ma X, Long L, Moon S, Adamson BJS, Baxi SS. Comparison of population characteristics in real-world clinical oncology databases in the US: Flatiron Health, SEER, and NPCR. medRxiv. May 30. doi: 10.1101/2020.03.16.20037143 [preprint, not peer-reviewed].
5. Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res. 2021;56(6):1281-1287.
6. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol. 2015;170(4):504-514.
7. Rosenwald A, Bens S, Advani R, et al. Prognostic significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol. 2019;37(35):3359-3368.