Cured and Invisible? Rationale for Mixture-Cure Models as Base-Case for HTA in Diffuse-Large B-Cell Lymphoma (DLBCL)

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CONCLUSIONS

- DLBCL is a curable disease and patients in long-term remissions might be - in general - considered "statistically cured."
- For curable diseases MCMs provide a more accurate survival estimates compared to standard parametric functions.
- Integration of MCMs into the decision framework will allow to better reflect the impact of innovative medicines during HTA.
- Correct assumptions allow tailoring of the model to mitigate potential bias.

BACKGROUND & OBJECTIVES

Mixture-cure models (MCMs) allow overcoming the reliability issues that traditional survival analysis methods face in the presence of statistical cure. In its recent decision, the Czech HTA body refused to accept this approach based on the assumption of different mortality rates between "cured" patients and normal population, which led to neglecting the presence of statistically cured patients and underestimation of the long-term survival. Therefore, here we aimed to analyze and discuss existing evidence related to the cure assumption and mortality of presumably cured DLBCL patients.

DLBCL CAN BE CURED WHEN TREATED EARLY

As a result of systematic literature search in PubMed® database we found 168 publications (see below for search query), from which we selected 37 manuscripts during abstract screen. Subsequently, we performed full text screen that yielded ten relevant publications comparing mortality of patients with DLBCL to the general population.

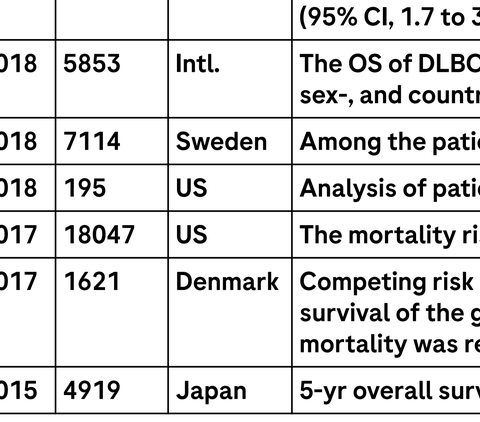
Ref.	Year	Sample size	Country	Results/conclusions
1	2023	507	France	Excess of mortality hazard five years after the treatment is almost null (even in patients with a poor prognosis), thus first-line DLBCL patients do not experience an increased mortality compared to the general population in the long-term follow-up.
2	2021	1169	Sweden	In the younger patients group with DLBCL treated with (R)-CHOP or R-CHOP-like regimens with curative intent (<59 yrs), overall survival (OS) matched that of their peers in the standard population. The OS for patients in the age interval 60–69 yrs was worse compared to the standard population (SMR of 1.65 (95% CI 1.09–2.18)) and similarly for the group 70–79 yrs (SMR of 1.19 (95% CI 0.88–1.47)). OS for patients aged >80 yrs matched that of their peers (SMR of 0.96 (95% CI 0.66–1.21)).
3	2021	5817	Japan	SMRs of patients with DLBCL after their first hematopoietic stem cell transplantation (HSCT) were significantly higher than that of the general population even after achieving EFS24 or EFS60. The SMRs of those after auto-HSCT were 2.5 to 3.5.
4	2019	371	US	SMR of patients with R/R DLBCL undergoing autologous hematopoietic cell transplantation was 4.0 (95% CI, 3.2 to 5.1) for 1-yr survivors, 3.0 (95% CI, 2.2 to 4.0), for 2-yr survivors, 2.4 (95% CI, 1.7 to 3.4) for 3-yr survivors, and 1.8 (95% CI, 1.1 to 2.9) for 5-yr survivors. With increased time, SMR decreased.
5	2018	5853	Intl.	The OS of DLBCL patients who are alive without progression at 24 months from the onset of initial therapy was marginally lower than, but clinically indistinguishable from the age-, sex-, and country-matched background population for at least 5 to 7 yrs after achieving PFS24.
6	2018	7114	Sweden	Among the patients <50 yrs at diagnosis who reached OS24, the remaining life expectancy of these patients was no longer significantly different from that of the general population.
7	2018	195	US	Analysis of patients with DLBCL alive 36 month after the diagnosis showed no significant excess mortality risk compared to matched background population (SMR 3.1 [0.8-8.0]).
8	2017	18047	US	The mortality risks were high within the initial 5 yrs after the diagnosis and declined after 5 yrs - total noncancer causes of death with SMR = 0.99 95% CI (0.88-1.10).
9	2017	1621	Denmark	Competing risk model using death from relapsed DLBCL as a competing event to death from other causes showed that the survival of patients with DLBCL was equivalent to the survival of the general population at the end of treatment. Therefore, the observed excess mortality in patients with DLBCL might be fully explained by early and late relapse. Excess mortality was reduced for patients achieving EFS24 (SMR of 1.27; P < .001) and normalized to the general population for patients reaching EFS24 and < 50 years of age (P = .99).
10	2015	4919	Japan	5-yr overall survival rate of DLBCL patients who survived 5 years from diagnosis was 87%, which indicates higher mortality compared with the general population.

Although some authors observed significant differences in mortality and long-term survival between patient and general population, in the majority of cases patients in the long-term remission (>2-5 yrs) experienced comparable or clinically indistinguishable survival compared to the general population. Therefore, we conclude that the existing evidence support the assumption of curability of patients with DLBCL, ie. presence of the fraction of the patient population that is considered statistically cured, with the same mortality as the general population, which is the basic requirement for application of mixture-cure models.

DLBCL PATIENTS "CURED" in 1L HAVE MORTALITY COMPARABLE with GENERAL POPULATION (based on RWD from the Czech clinical practice)

Based on the analysis of RWD of Czech patients with newly diagnosed systemic DLBCL between years 2010–2019 from the database of prospective project NiHiL (NCT03199066) receiving R-CHOP (A), we estimated the overall survival (OS) of patients that achieved long term remission defined as the interval from the end of the first-line therapy to the date of progression, relapse, initiation of second line treatment or death from any cause) at 24 months (EFS24) - i.e. remained event-free at 24 months after the end of the first-line treatment (B) by using landmark survival comparison based on Kaplan-Meier method. For these patients, we computed the OS landmark point as the date of diagnosis plus duration of therapy plus 24 months. For the general population, we computed it as the date of contact with health-care system plus 24 months.

(A)



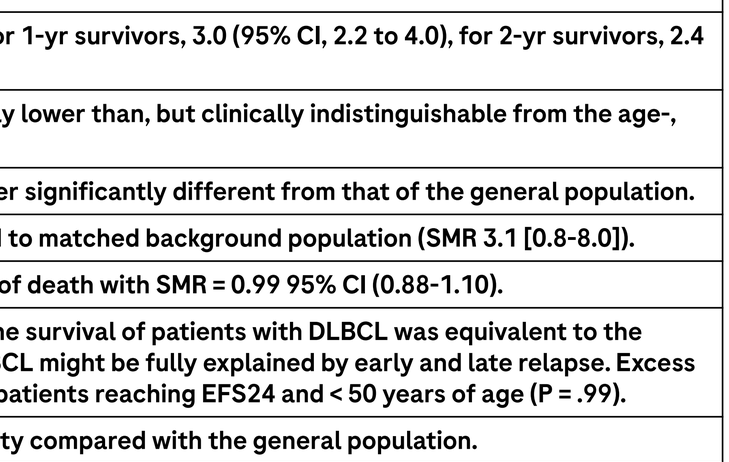
(B)

	n	
Patients included	1,594	
Median age (range)	65	(17–88)
Age category	1,594	
≤ 60 years	581	36%
> 60 years	1,013	64%
Gender	1,594	
male	840	53%
Ann Arbor stage	1,587	
I or II	826	52%
III or IV	761	48%

	n	
No. of extranodal sites	1,590	
0	510	32%
1	648	41%
≥ 2	432	27%
Bulky disease ≥ 7.5 cm	1,359	
yes	503	37%
ECOG PS	1,588	
0 or 1	1,257	79%
2	221	14%
3 or 4	110	7%

	n	
LDH level	1,574	
elevated	870	55%
IPI score	1,561	
low	574	37%
low-intermediate	350	22%
high-intermediate	327	21%
high	310	20%
Cell of origin	766	
non-GCB	337	44%
Diagnosis to treatment, days (interquartile range)	28	(16–43)

(C)



(A) Comparison of real-world survival data of patients from Czech clinical practice - study design; (B) Baseline characteristics of the EFS24 patients; (C) Age- and sex-matched comparison of overall survival of patients with diffuse large B-cell lymphoma with EFS24 with general population in the Czech Republic (P = 0.06).

As a result, we found out that the OS of DLBCL patients with EFS24 didn't statistically differ from the general population (mean OS 8.244 years vs. 8.236 years; P = 0.06) in the real-world setting (C).

MCMs BECOME ACCEPTED for HTA (NICE)

- **Polatuzumab vedotin in 1L [TA874]**
  - 'cured' population - the same risk of death as matched general population after 2 yrs
  - MCM concluded as a reasonable approach
- **Axicabtagene ciloleucel in 2L [TA895]**
  - people with EFS at 5 yrs are effectively cured
- **Axicabtagene ciloleucel in 2+L [TA872]**
  - responders were assumed to have a same mortality rate as the general population
  - durable responses in a minority of people after CAR-T -> the plateau present in the extrapolations seemed reasonable

TOWARDS MORE RELIABLE MODELLING (TO BE CONTINUED)...

- Among tested statistical methods (standard parametric survival, landmark, spline and mixture-cure models), latter one provided the best prediction of long-term outcomes from the final PFS analysis of the POLARIX study (11)
- Comparison of MCM with standard parametric models using data from the GO29365 study (R/R DLBCL) showed that MCM predictions were best aligned with observed survival data from the clinical trial (12)
- MCMs help reduce bias in OS estimates and provide more accurate estimates in presence of "cured" patients (13)
- In case of highly uncertain assumptions more conservative approach can be considered - e.g. by applying mortality adjustments for "statistically cured" patients (14,15)

SLR SEARCH QUERY

(("DLBCL"[All Fields] AND ("cure*"[All Fields] OR "curable"[All Fields] OR "long term remission"[All Fields] OR "SMR"[All Fields] OR "general population"[All Fields] OR "matched population"[All Fields] OR "standardized mortality ratio"[All Fields])) NOT ("review"[All Fields] OR "case"[All Fields] OR "Cureus"[Journal] OR "bioRxiv"[Journal])) AND (y_10[Filter])

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