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TRAIL Score: A Simple Model to Predict Immunochemotherapy Tolerability in Patients With Diffuse Large B-Cell Lymphoma

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PURPOSE Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) represents the standard of care for first-line treatment of diffuse large B-cell lymphoma (DLBCL). However, many patients are unable to tolerate R-CHOP and have inferior outcomes. This study aimed to develop a practical tool to help physicians identify patients with newly diagnosed DLBCL unlikely to tolerate a full course of R-CHOP.

METHODS We developed a predictive model (Tolerability of R-CHOP in Aggressive Lymphoma [TRAIL]) on the basis of a training data set from the phase III GOYA trial (obinutuzumab with CHOP *v* R-CHOP in 1L DLBCL) using a composite binary end point, identifying patients who prematurely stopped or required reductions of R-CHOP. Candidate predictive variables were selected on the basis of known baseline characteristics that contribute to patient frailty, comorbidity, and/or chemotherapy toxicity. TRAIL was developed using an iterative trial-and-error modeling process to fit a logistic regression model. The final model was evaluated for robustness using a GOYA holdout data set and the phase III MAIN (R-CHOP with or without bevacizumab in 1L DLBCL) R-CHOP-21 data set as external validation.

RESULTS TRAIL includes four simple predictors available in the routine clinical setting: Charlson Comorbidity Index, presence of cardiovascular disease or diabetes, serum albumin, and creatinine clearance. Model generalization performance estimated by the area under the curve was around or above 0.70 across GOYA training, GOYA holdout, and MAIN data sets. Classifying patients into low-, intermediate- and high-risk categories, the proportion of patients experiencing a tolerability event was 3.3%, 12.4%, and 32.9%, respectively, in GOYA holdout, and 9.7%, 9.7%, and 34.2%, respectively, in MAIN.

CONCLUSION TRAIL may be useful as a clinical decision support tool for treatment decisions in patients with DLBCL who may not tolerate standard chemoimmunotherapies.

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INTRODUCTION

Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is the standard first-line treatment for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL).[1-3] Treatment with six to eight cycles of R-CHOP has been demonstrated to be efficacious for the majority of patients, with 60%-70% of those commencing this treatment achieving durable remissions.[3,4]

Although R-CHOP has been the mainstay of DLBCL treatment for more than 2 decades, this regimen is associated with significant toxicity and many patients, especially those who are elderly, present with a reduced physiologic reserve and often comorbidities that may preclude full-dose R-CHOP.[5-8] Among patients age > 66 years with newly diagnosed non-Hodgkin's lymphoma in the SEER-Medicare database, 52% of patients had ≥ 1 comorbidity and 26% had a Charlson Comorbidity Index > 2.[9] The most prevalent comorbidities were diabetes (25%), chronic obstructive pulmonary disease (16%), and congestive heart failure (12%).[9] In a retrospective cohort study of approximately 18,000 patients age 66 years and older, diagnosed with DLBCL between 2001 and 2013 in the SEER-Medicare database, patients age > 80 years were reported to be less likely to receive R-CHOP as a first line of therapy compared with patients age 66-80 years (46.5% in patients > 80 years *v* 71% in patients up to 80 years).[10]

Outcomes have been found to be inferior in patients who do not complete R-CHOP therapy.[11] In a retrospective, single-center study of 115 previously untreated patients, Kwak et al[12] identified an actual relative dose intensity of doxorubicin > 75% as the single most important predictor of survival in DLBCL.

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) represents the standard of care for first-line treatment of diffuse large B-cell lymphoma; however, many patients are unable to tolerate R-CHOP and have inferior outcomes. This analysis involved developing a simple model to identify patients who are at high risk of not tolerating R-CHOP–based therapies and may be of particular relevance for elderly patients with or without comorbidities.

Knowledge Generated

A simple model to predict R-CHOP toxicity was developed, the Tolerability of R-CHOP in Aggressive Lymphoma score, consisting of the following routinely collected clinical laboratory results and medical history: albumin levels, creatinine clearance, Charlson Comorbidity Index, and an indicator of whether the patient has cardiovascular or diabetes comorbidities. This model showed superior performance to other commonly used prognostic factors for chemotherapy tolerability such as age, International Prognostic Index, and Eastern Cooperative Oncology Group in two validation data sets.

Relevance

The Tolerability of R-CHOP in Aggressive Lymphoma score is a simple model that can be easily applied in a clinical setting to predict a patient's risk of R-CHOP chemotoxicity.

Of 3,149 adult patients with newly diagnosed DLBCL between 2007 and 2014 from the Swedish Lymphoma Register, 10% of patients did not complete their planned treatment for reasons other than lack of response.[11] Patients who stopped treatment after one to three cycles or after four to five cycles had a 5-year overall survival (OS) of 26% (95% CI, 19 to 33) and 49% (95% CI, 41 to 57) compared with 76% (95% CI, 74 to 77) in patients who received at least six cycles of treatment. Risk factors associated with premature discontinuation of R-CHOP therapy included advanced age, poor performance status, elevated lactate dehydrogenase levels, presence of extranodal disease, and stage IV disease.[11] Similar results were seen in another observational population-based cohort study.[7] Among 70 patients with DLBCL age ≥ 75 years treated with R-CHOP, 39 completed the planned course of treatment. The 2-year OS for patients who completed all R-CHOP cycles was 70% versus 28% in patients who received less than full treatment with R-CHOP or other less intensive chemotherapeutic regimens.[7] Furthermore, a study of survival in elderly patients with DLBCL age ≥ 80 years from a Swedish Lymphoma Register study demonstrated that 2-year OS was greater in patients given treatment with curative intent (54%) than those receiving low-intensity treatment (26%).[13] This highlights the importance of identifying those patients who may be older but who may still benefit from intensive therapy.

Given these observed inferior outcomes in patients who cannot tolerate full treatment with standard R-CHOP, it is clinically relevant to identify this group of patients as early as possible to consider them for clinical trials. In a retrospective analysis conducted in an older Australian patient cohort (patients with DLBCL age ≥ 75 years), R-CHOP was administered to 83% of patients, which may reflect consideration of patient fitness and physician and patient willingness to try R-CHOP therapy at the time of treatment initiation.[14] Among the patients treated with R-CHOP, at least six cycles were administered in 62% of patients despite significant toxicity, with 74% experiencing adverse events (AEs) leading to death or requiring hospitalization. As such, treatment decisions in elderly patients may be better informed by a tool to support pretreatment identification of patients who are unlikely to tolerate R-CHOP therapy.

In this study, we analyzed patients from the GOYA (NCT01287741)[15] and MAIN (NCT00486759)[16] trials to delineate factors associated with poor R-CHOP tolerability in patients with DLBCL. GOYA and MAIN are two of the largest 1L DLBCL clinical trials testing R-CHOP versus obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and R-CHOP with and without bevacizumab, respectively. Furthermore, patient population (1L DLBCL) and treatment schedules (using R-CHOP) were comparable between both trials and both had near complete data available. At the time of this analysis, there were no other contemporaneous trial data with comparable population, population size, outcome, and study design available to the authors. The aim was to develop a model (Tolerability of R-CHOP in Aggressive Lymphoma [TRAIL]) to predict the risk of intolerability to R-CHOP induction therapy using variables captured at baseline and validate it using data from GOYA and from patients receiving 21-day cycles of R-CHOP in the external independent MAIN study.

METHODS

Study Design and Data

Data for model development were obtained from the multicenter, open-label, randomized phase III GOYA trial (NCT01287741). Patients with DLBCL were recruited from 207 centers in 29 countries between July 2011 and June 2014. Eligible patients were age ≥ 18 years, previously

untreated, and diagnosed with CD20-positive DLBCL. Other inclusion criteria included the following: an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-2; adequate hematologic, liver, and kidney function; a left ventricular ejection fraction of ≥ 50%; and no significant, uncontrolled concomitant diseases. Further details of the inclusion and exclusion criteria have been previously reported.[15,17] Patients in GOYA were treated with either six or eight 21-day cycles of R-CHOP or obinutuzumab plus CHOP. The median follow-up at the time of the final analysis (January 2018) was 48 months.[17] Since there was no statistical difference in outcomes detected between the obinutuzumab and rituximab treatment arms in GOYA, the data from both arms were pooled for this analysis.

Data for external validation were obtained from the multicenter, randomized, double-blind, placebo-controlled phase III MAIN study (NCT00486759). In total, 186 centers, located in 30 countries, participated in MAIN and recruited patients age ≥ 18 years with previously untreated DLBCL between July 2007 and May 2010. This trial was designed to compare R-CHOP with and without bevacizumab.[16] Investigators participating in MAIN at the study site level predefined patients to follow a 14- or a 21-day cycle of CHOP chemotherapy. Treatment with additional bevacizumab was blinded by placebo infusions in addition to R-CHOP. Further details of study treatment are previously published.[16] The trial was stopped early by sponsor decision because of increased cardiotoxicity and no prolongation of progression-free survival in the bevacizumab arm. The median durations of follow-up for the R-CHOP and R-CHOP in combination with bevacizumab arms were 23.7 and 23.6 months, respectively. Because of the safety signals observed in the bevacizumab arm and the known increased toxicity associated with CHOP in 14-day cycles (CHOP-14), only data from patients treated with R-CHOP for 21-day cycles (R-CHOP-21) in MAIN were used here for model validation.

Both trials were conducted according to the Declaration of Helsinki and were approved by institutional review boards and/or ethics committees at all sites. Written informed consent was provided by all patients.

For the purpose of this analysis, the composite tolerability end point (intolerability to CHOP) was defined as the occurrence of at least one of the following events within the first six cycles: AE leading to withdrawal of cyclophosphamide and/or doxorubicin before completion of six cycles, death without disease progression, or average dose intensity of cyclophosphamide and doxorubicin < 80% not related to disease progression. The rationale for choosing an end point on the basis of these components is that it identifies those patients not receiving an optimal dose intensity of CHOP chemotherapy because of poor tolerability.

Model Development and Validation

Candidate predictor variables used for model development were baseline characteristics known to contribute to patient frailty, comorbidity, and/or chemotherapy toxicity. These included demographics, pretreatments, medical history, laboratory values, and patient-reported outcomes. All predictors were measured before the initiation of treatment. Missing data were not imputed for this analysis for predictors or end points, and thus, all analyses are on complete observed cases.

Model evaluation. Statistical modeling was performed retrospectively using data from the GOYA safety-evaluable population (N = 1,407). The GOYA data were divided into a 75% training set (n = 1,051), used for model training and cross-validation, and a 25% holdout set (n = 356) that was blinded to the analysis team to serve as a test set for validation. The training set was divided into four folds for cross-validation, each including between 260 and 265 patients. These four folds and the holdout set were created in a way to achieve a balanced distribution of the following variables: immunotherapy group, International Prognostic Index (IPI) category, progression-free survival event, and sum of product diameters of lymphoma lesions. To obtain splits for four-fold cross-validation and internal validation, data from GOYA were split into five folds with four folds selected as training data and one fold as holdout data. Generation of folds followed the approach of a Nested Repeated Balanced Cross-Validation; see the Data Supplement for additional information. Random 10-fold cross-validation and bootstrapping using the GOYA training data were additionally used to assess model performance.

Model development included the following tasks: evaluation of correlation between individual predictor variables and outcomes, examination of predictor distributions, creation of transformed predictors if indicated, and finally, a series of model evaluation stages. All the following steps, before model validation, were performed on the GOYA training data only.

Predictor screening. The associations between candidate covariates and the composite end point were initially investigated to identify highly prognostic predictors and to attempt to construct informative variables. Pearson product-moment correlations (with 95% CI and *P* values) were evaluated between each predictor and the composite end point. The correlations between predictors and the individual components of the composite end point were used for the predictor selection, and correlations between each pair of individual predictors were also evaluated.

Predictor construction. As a consequence of the correlation analysis, univariate predictor distributions were further analyzed to construct informative variables. Distributions of candidate predictor variables were examined, and a variety of transformations were considered, eg, categorizing continuous variables and evaluating nonlinear transformations (square root, log, and Box-Cox). To assess the predictive value of each predictor variable, we implemented a novel

ranking algorithm, GameRank.[18] Details of these approaches can be found in the Data Supplement.

Model development. Determination of the final model for prediction was an iterative process. Starting with a set of initial models on the basis of highly correlated predictors, a trial-and-error modeling process was followed to improve the cross-validated area under the curve (AUC) and the bootstrap optimism. Bootstrapped estimates for model generalization error and optimism were obtained using the 0.632 method.[19] Variable importance was determined using GameRank, and their included predictors were compared on the basis of the AUC of the receiver operating characteristic (ROC).[20] Details for these procedures are given in the Data Supplement. After the model was selected, the contribution of each predictor was evaluated and the availability of predictors in the clinical setting was also considered for predictor selection.

Independent validation. Ultimately, the final candidate models were selected, fit on the complete GOYA training data, and evaluated on the GOYA holdout and MAIN external validation data sets. The final models were evaluated on the basis of the AUC of the ROC.[20] To confirm that the predicted probability score reflects the observed rate of positive events in independent validation sets, calibration curves were generated using the GOYA holdout and MAIN external validation data sets. Further details of the model calibration are provided in the Data Supplement.

Risk categories. To facilitate the use of the TRAIL model in a clinical research setting, risk categories were defined to convert a continuous score into categorical classifications for intolerability to R-CHOP. Cutoffs for risk categories were defined on the basis of quartiles for probability of the tolerability event using the GOYA training data. A probability less than quartile one (Q1) was considered low risk, a probability greater than or equal to Q3 was considered high risk, and probabilities between Q1 and Q3 were considered intermediate risk. This three-category approach was driven by the desire to discriminate patients with either very high or very low probability of tolerating R-CHOP or G-CHOP. The stability of these cutoffs was evaluated across cross-validation folds. The final cutoffs were locked before independent validation on the GOYA holdout and MAIN external validation sets. Further information on defining risk groups is provided in the Data Supplement.

RESULTS

Key baseline characteristics of patients in GOYA and MAIN R-CHOP-21 are provided in Table 1. Patient populations were broadly similar with regard to key characteristics. Participant flowcharts for GOYA and MAIN R-CHOP-21 are summarized in Figure 1.

A Venn diagram for components of the composite tolerability end point in patients in the overall GOYA population is presented in Figure 2A. The composite tolerability end point occurred in 188 of 1,407 (13.4%) patients. The majority of these were low average relative dose intensity of cyclophosphamide and doxorubicin. For patients with the reduced dose intensity component of the tolerability outcome, the median average dose intensity of cyclophosphamide and doxorubicin was 52.3% in GOYA and 48.0% in MAIN R-CHOP-21. The majority of deaths within the first six cycles of therapy in GOYA were AE-related (19 of 22 [86.4%] patients), and all five deaths were AE-related within the first six cycles of therapy in MAIN R-CHOP-21. The most common cause of AE-related death in both trials was infection. Correlation analysis between predictor variables and the tolerability end point did not identify any predictor with the correlation > 0.2 for either outcome or its components. The corresponding Venn diagram for the MAIN R-CHOP-21 population is presented in Figure 2B. The composite tolerability end point occurred in 47 of 312 (15.1%) patients.

The final logistic regression model was chosen at the end of model development for its combination of prognostic ability, simplicity, and clinical utility. This model (TRAIL) is presented in Table 2. In the full GOYA data set, 1,374 of 1,407 (97.7%) safety-evaluable patients had non-missing data for all four covariates in the final model. In the MAIN validation data set, 300 of 312 (96.2%) safety-evaluable R-CHOP-21 patients had nonmissing data for all four covariates in the final model. The final model was fit to a training cohort from GOYA comprising N = 1,022 patients having complete data with 132 (12.9%) events. It reached the AUC (95% CI) of 0.700 (0.652 to 0.749) on the GOYA training data, 0.722 (0.647 to 0.797) on the GOYA holdout data, and 0.691 (0.604 to 0.778) on the MAIN external validation data. Further details of this final prediction model are provided in the Data Supplement.

ROC curves for the TRAIL model are shown in Figure 3A using the GOYA training, GOYA holdout, and MAIN external validation data. ROC curves for the TRAIL model compared with the established prognostic factors such as age, IPI, and ECOG PS using the GOYA holdout and MAIN external validation data are shown in Figure 3B. AUC was consistently higher for TRAIL than for clinical risk factors expected to be associated with tolerability in both GOYA and MAIN. The percentage of patients experiencing a tolerability event by risk category is presented in Figure 4. Cutoffs for low-, intermediate-, and high-risk categories were defined on the basis of quartiles of predicted probabilities (low risk [0, 0.07], intermediate risk [0.07, 0.16], and high risk [0.16, 1]). In the GOYA holdout data set, the proportion of patients experiencing a tolerability event was 3.3% in the low-risk, 12.4% in the intermediate-risk, and 32.9% in the high-risk group (Data Supplement). The corresponding proportions for MAIN were 9.7%, 9.7%, and 34.2%, respectively (Data Supplement). Kaplan-Meier plots of OS stratified by risk category are presented in Figure 5. The 4-year OS in the GOYA holdout data set was 90.7% in the low-risk group, 80.2% in the intermediate-risk group, and 69.2% in the high-risk group.

TABLE 1. Key Baseline Demographics and Clinical Characteristics of Patients in the GOYA and MAIN R-CHOP-21 Data Sets

Characteristic	GOYA Training (n = 1,051)	GOYA Holdout (n = 356)	GOYA Safety-Evaluable Population (N = 1,407)	MAIN R-CHOP-21 (N = 312)
Age, median (IQR), years	62 (17)	61 (19)	62 (17)	59 (20)
Age, No. (%), years				
≤ 65	665 (63.3)	234 (65.7)	899 (63.9)	203 (65.1)
> 65	386 (36.7)	122 (34.3)	508 (36.1)	109 (34.9)
Sex, male, No. (%)	560 (53.3)	184 (51.7)	744 (52.9)	157 (50.3)
IPI, No. (%)				
0	24 (2.3)	6 (1.7)	30 (2.1)	11 (3.5)
1	195 (18.6)	56 (15.7)	251 (17.8)	42 (13.5)
2	365 (34.7)	135 (37.9)	500 (35.5)	124 (39.7)
3	305 (29.0)	103 (28.9)	408 (29.0)	93 (29.8)
4	131 (12.5)	51 (14.3)	182 (12.9)	38 (12.2)
5	31 (3.0)	5 (1.4)	36 (2.6)	4 (1.3)
ECOG PS, No. (%)[a]	*1,051*	*355*	*1,406*	*310*
0	495 (47.1)	153 (43.1)	648 (46.1)	126 (40.7)
1	426 (40.5)	148 (41.7)	574 (40.8)	117 (37.7)
2	129 (12.3)	53 (14.9)	182 (12.9)	66 (21.3)
3	1 (0.1)	1 (0.3)	2 (0.1)	1 (0.3)
Ann Arbor stage, No. (%)[a]	*1,051*	*356*	*1,407*	*305*
I	80 (7.6)	21 (5.9)	101 (7.2)	28 (9.2)
II	169 (16.1)	69 (19.4)	238 (16.9)	56 (18.4)
III	343 (32.6)	118 (33.2)	461 (32.8)	103 (33.8)
IV	459 (43.7)	148 (41.6)	607 (43.1)	118 (38.7)
Treatment, No. (%)				
G-CHOP	525 (49.95)[b]	178 (50.0)	703 (50.0)	0 (0.0)
R-CHOP	526 (50.05)[b]	178 (50.0)	704 (50.0)	312 (100.0)
Composite outcome, No. (%)				
Event	134 (12.75)[b]	54 (15.2)	188 (13.4)	47 (15.1)
No event	917 (87.25)[b]	302 (84.8)	1,219 (86.6)	265 (84.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; G-CHOP, obinutuzumab with cyclophosphamide, doxorubicin, vincristine, and prednisone; IPI, International Prognostic Index; IQR, interquartile range; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone.

[a]Number of patients with data available.

[b]Provided to two decimal places because of rounding.

In the GOYA holdout data set, 74.1% of patients reported a treatment-emergent grade 3-5 AE in the high-risk category compared with 70.1% in the intermediate-risk and 65.6% in the low-risk category (Data Supplement). The corresponding proportions for MAIN were 74.0%, 57.5%, and 48.4%, respectively (Data Supplement). A greater proportion of patients in the intermediate- and high-risk TRAIL categories experienced grade 4 and 5 AEs compared with the low-risk group.

DISCUSSION

The goal of the current study was to develop a simple and practical model to predict the risk of patients diagnosed with DLBCL not tolerating R-CHOP, using readily available data before initiation of treatment. Across the GOYA training and holdout data and the external MAIN data, the generalization performance, as estimated by the AUC, was consistently around or above 0.70. The TRAIL model is based on a logistic regression that returns well-calibrated predictions. Overall, the calibration curves for all GOYA training, GOYA holdout, and MAIN external validation data sets show that the predicted probabilities of a tolerability event, defined as death, dose reduction, or withdrawal because of AE during the R-CHOP treatment period, are well matched with the observed rate. It is notable that for the GOYA holdout and MAIN external validation data sets, the TRAIL model performed better than common prognostic factors for tolerability such as age and ECOG PS and also better than IPI.

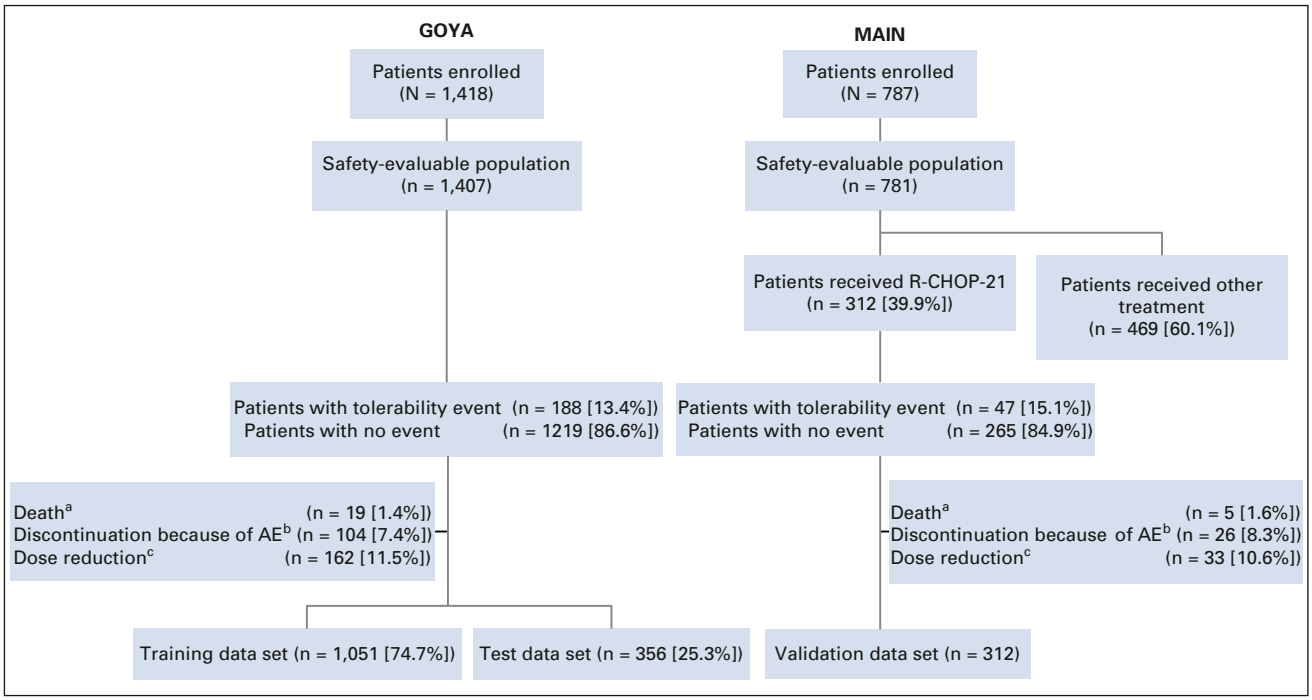

FIG 1. Patient flowchart in the GOYA and MAIN R-CHOP-21 studies. AE, adverse event; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone. [a] Death within 6 cycles not related to PD. [b] AE leading to withdrawal of cyclophosphamide/doxorubicin. [c] Average dose intensity of cyclophosphamide/doxorubicin within 6 cycles less than 80%, not related to PD.

The model was selected as a trade-off between prognostic performance, clinical utility, and simplicity. It includes four simple variables, which can all be readily obtained in routine clinical practice. The four TRAIL risk features, Charlson Comorbidity Index, presence of cardiovascular disease or diabetes, low serum albumin, and low creatinine clearance, are frequently observed in patients with DLBCL. For example, Laribi et al[21] reported that in a population of frail patients age ≥ 80 years with DLBCL, about 60.5% had a Charlson Comorbidity Index ≥ 4, 41.9% had an ECOG PS of 3, and 53.5% presented with low creatinine clearance. The four selected risk features have also consistently been found to be independently associated with reduced OS in DLBCL.[22-25] Although further research is certainly warranted, these reports further underpin the predictor selection proposed in this analysis.

The importance of pretreatment evaluation of patients to ascertain frailty and potential tolerance to therapy has been highlighted by the National Comprehensive Cancer Network[2] and the Society of Geriatric Oncology taskforce.[26] The Society of Geriatric Oncology considered that evaluation by performance status alone is insufficient, especially in elderly patients, and recommended inclusion of comorbidities and functional and/or social decline in such assessments. Various tools have been developed to assess the risks of chemotherapy or to define frail patients, including the Cancer and Aging Research Group (CARG) risk score (for patients older than 65 years diagnosed with solid tumors)[27] and the Chemotherapy Risk Assessment Scale for High-Age patients (CRASH) score.[28] The CARG predictive model achieved an AUC of 0.65 for predicting grade 3-5 toxicities in their independent sample.[27] This score classified patients as having low, intermediate, or high risk of chemotherapy intolerability. The validation set classified 24%, 53%, and 23% as low, intermediate, and high risk, with the associated risk of grade 3-5 toxicity of 30%, 52%, and 83%, respectively.[27] Similarly, the CRASH score, which was developed to predict grade 4 hematologic and grade 3 and/or 4 nonhematologic toxicities regardless of cancer treatment in patients older than 70 years, showed a C-statistic (95% CI), which equivalent to the AUC of 0.64 (0.56 to 0.72) in their independent sample.[28] A disease-specific tool to predict the probability of chemotherapy toxicity has been developed for elderly adults (age ≥ 65 years) with early-stage breast cancer. The CARG Breast Cancer score was recently developed and validated to predict grade 3-5 chemotherapy toxicity and is based on eight clinical and geriatric factors.[29] The study found that the risk score may help to determine new strategies to mitigate the risk of chemotherapy toxicity. Neither of these chemotherapy toxicity predictors have been used to evaluate the risk of intolerance to a complete course of R-CHOP therapy in patients with DLBCL.

We have evaluated the TRAIL score relative to known existing prognostic factors in DLBCL. TRAIL outperforms commonly used prognostic indicators such as age, ECOG, and IPI in predicting chemotoxicity on our first-line DLBCL data sets. Chemotoxicity-specific scores such as CARG and

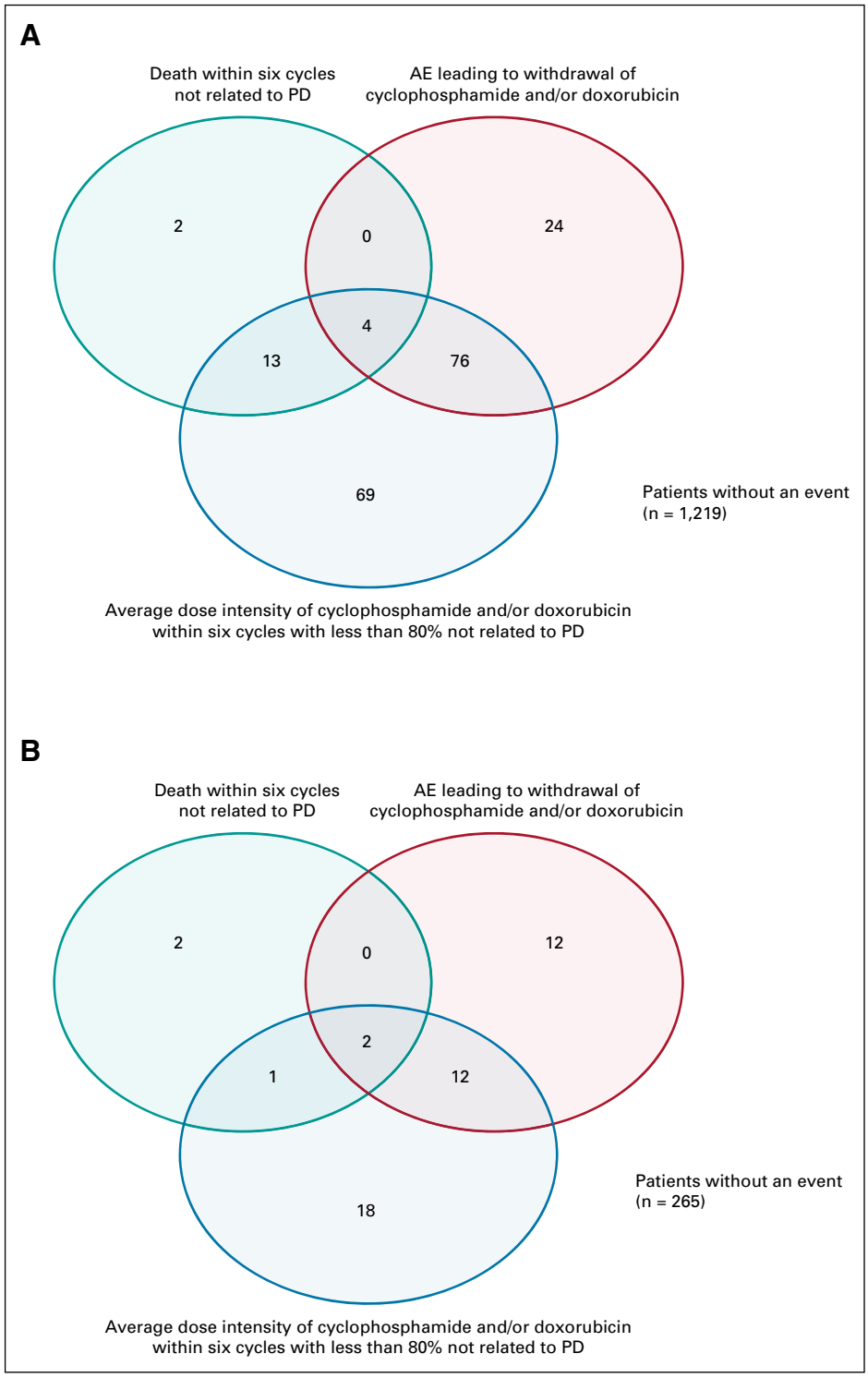

FIG 2. Venn diagrams of outcomes for those patients with a tolerability event in (A) GOYA and (B) MAIN rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone-21. The number of patients without an event is indicated. AE, adverse event; PD, disease progression.

CRASH could not be assessed in our data sets because of elements not routinely collected in clinical visits, for example, activities of daily living. However, TRAIL achieved higher AUCs than prior scores reported in their validation data sets. Although all of this is important, we want to remind readers that ultimately it is a prospective trial that will determine if clinical utility can be confirmed.

A study published by the Italian Lymphoma Foundation in 2015 used the Comprehensive Geriatric Assessment (CGA) to classify elderly patients age > 69 years with DLBCL into fit, unfit, and frail categories.[30] Patients in each category were given curative or palliative treatment on the basis of clinical judgment. The 2-year OS with curative versus palliative treatment was 88% versus 25% ($P = .0001$) in fit,

TABLE 2. Tolerability of R-CHOP in the Aggressive Lymphoma Logistic Regression Model

Covariate[a]	Parameter Estimate	95% CI	*P*
Intercept	5.45	1.65 to 9.20	.004
1/(creatinine clearance), mL/min	86.8	42.7 to 131.0	< .001
ln(albumin), g/L	–2.48	–3.51 to –1.43	< .001
Charlson Comorbidity Index score	0.170	–0.00121 to 0.340	.051
History of heart or vascular disease or diabetes	0.362	–0.151 to 0.864	.161

[a]Trained on N = 1,022 patients with complete cases for covariates and 132 patients (12.9%) with event.

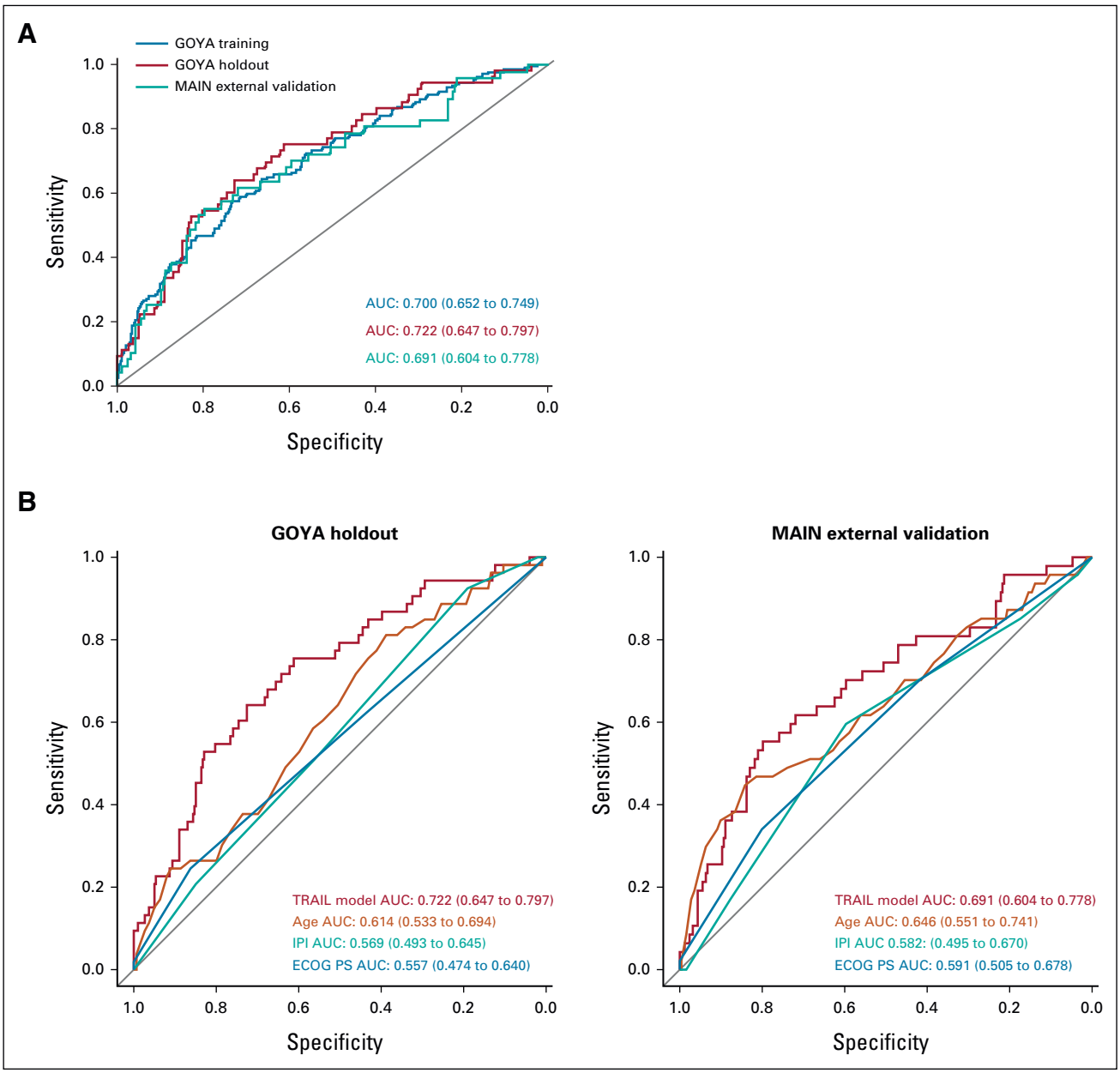

FIG 3. (A) ROC curves for the TRAIL model and AUC for the logistic regression models; (B) ROC curves for the TRAIL model compared with those for established prognostic factors (age, IPI, and ECOG PS) for both the GOYA holdout and MAIN external validation data sets. AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; ROC, receiver operating characteristic; TRAIL, Tolerability of R-CHOP in Aggressive Lymphoma.

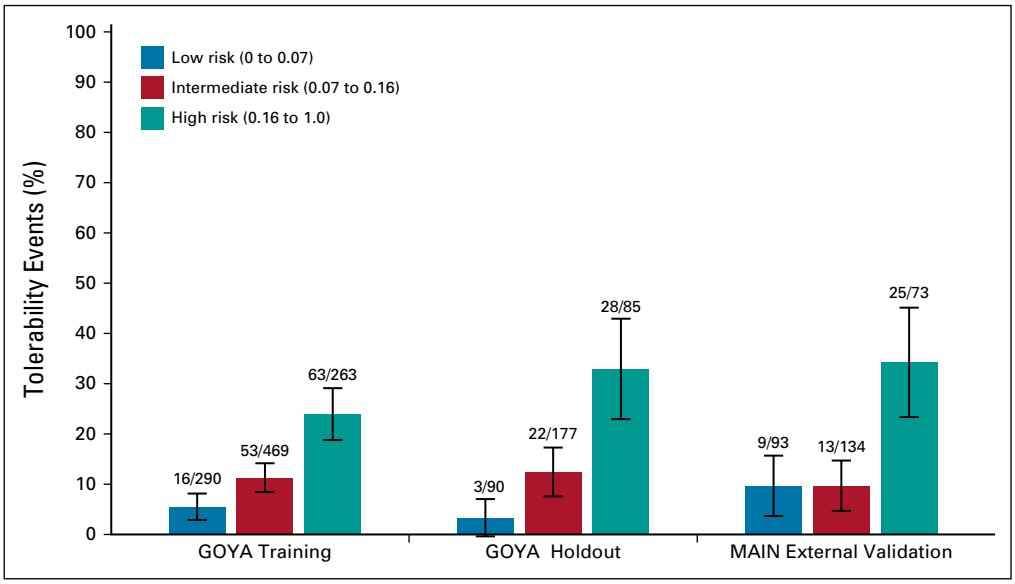

FIG 4. Proportion (%) of tolerability events (unable to tolerate CHOP in combination with rituximab or obinutuzumab) in the GOYA and MAIN data sets according to Tolerability of R-CHOP in Aggressive Lymphoma risk category. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

75% versus 45% ($P = .32$) in unfit, and 44% versus 39% ($P = .75$) in frail patients, suggesting that the CGA can be used to identify elderly patients who could benefit from a curative treatment.[30] The CGA, however, is rather time-consuming and not routinely used in clinical practice.

Importantly, the high performance of the final TRAIL model was achieved despite being developed in a clinical trial population excluding patients with severe comorbidities and clinically obvious conditions precluding full-dose CHOP. This approach supports clinical utility of the tool in that it identifies patients at high risk of a tolerability event in those patients who are considered candidates for CHOP-based therapies by the treating physician. However, the data used in these analyses stem from randomized controlled clinical trials and may not fully reflect the real-world patient population. Therefore, the model should be further validated in a broader population, more closely resembling the DLBCL population treated in clinical practice, including elderly patients.

In conclusion, we developed a simple, practical model (TRAIL) consisting of just four clinical variables to predict immunochemotherapy tolerability in patients with previously untreated DLBCL. This model has the potential to be used as a clinical decision support tool and may be of particular relevance in elderly patients. In the clinical setting, clinicians are often faced with the dilemma of prescribing full-dose R-CHOP treatment with the aim of achieving best possible disease control and cure chances versus limiting dose intensity to limit the risk of serious toxicities and preserve quality of life. Reduced intensity regimens, such as R-mini-CHOP, nonanthracycline regimens including rituximab monotherapy and rituximab-

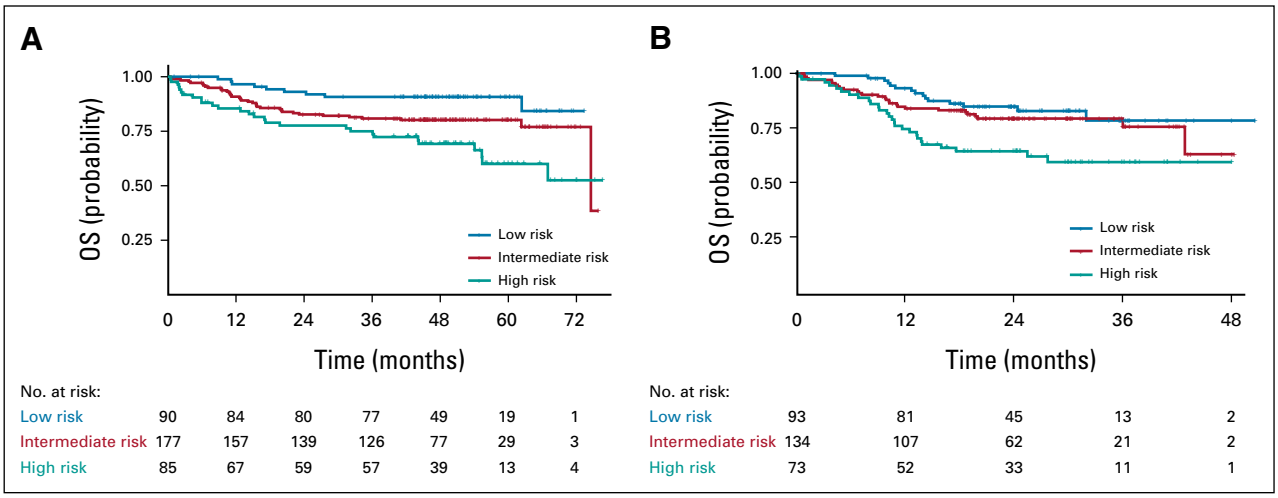

FIG 5. Kaplan-Meier analysis of OS according to Tolerability of R-CHOP in Aggressive Lymphoma risk group in (A) the GOYA holdout data set and (B) the MAIN external validation data set. OS, overall survival.

cyclophosphamide-vincristine-prednisone, or those substituting doxorubicin with gemcitabine or etoposide may be considered in these patients.[1,2,8] A number of clinical trials targeting elderly patients age ≥ 80 years or patients of advanced age (≥ 60 years) who have comorbidities and are not candidates for standard R-CHOP are currently underway. Novel regimens under investigation include lenalidomide and rituximab (NCT02955823), R-mini-cyclophosphamide, doxorubicin, and prednisone (CHP) with polatuzumab vedotin (NCT04332822), mosunetuzumab monotherapy (NCT03677154), and R2-mini-CHOP (NCT02128061). These novel approaches may enable elderly patients with DLBCL to receive tolerable and efficacious therapies in the future.

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available in https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, visit https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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