Evidence of cure for extranodal nasal-type natural killer/T-cell lymphoma with current treatment: an analysis of the CLCG database

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Abstract

Survival from extranodal nasal-type NK/T-cell lymphoma (ENKTCL) has substantially improved over the last decade. However, there is little consensus as to whether a population of patients with ENKTCL can be considered “cured” of the disease. We aimed to evaluate the statistical “cure” of ENKTCL in the modern treatment era. This retrospective multicentric study reviewed the clinical data of 1,955 patients with ENKTCL treated with non-anthracycline-based chemotherapy and/or radiotherapy in the China Lymphoma Collaborative Group multicenter database between 2008 and 2016. A non-mixture cure model with incorporation of background mortality was fitted to estimate cure fractions, median survival times and cure time points. The relative survival curves attained plateau for the entire cohort and most subsets, indicating that the notion of cure was robust. The overall cure fraction was 71.9%. The median survival was 1.1 years in uncured patients. The cure time was 4.5 years, indicating that beyond this time, mortality in ENKTCL patients was statistically equivalent to that in the general population. Cure probability was associated with B symptoms, stage, performance status, lactate dehydrogenase, primary tumor invasion, and primary upper aerodigestive tract site. Elderly patients (>60 years) had a similar cure fraction to that of younger patients. The 5-year overall survival rate correlated well with the cure fraction across risk-stratified groups. Thus, statistical cure is possible in ENKTCL patients receiving current treatment strategies. Overall probability of cure is favorable, though it is affected by the presence of risk factors. These findings have a high potential impact on clinical practice and patients’ perspective.

Introduction

Extranodal nasal-type NK/T-cell lymphoma (ENKTCL) is an aggressive and heterogeneous disease with variable prognosis. It is globally rare but relatively more common in East Asia and South America.[1] ENKTCL frequently originates from the upper aerodigestive tract (UADT), and most patients (70-90%) present with early-stage disease.[2,3] Survival outcomes for ENKTCL have substantially improved over the last decade, owing to the use of upfront modern radiotherapy[4-8] and non-anthracycline (ANT)-based chemotherapy,[9-13] establishment of novel prognostic models,[14-16] and risk-adapted treatment strategy.[7,17] The 5-year overall survival (OS) rates range from 55% to 90% for low- and intermediate- to high-risk early-stage disease,[12-15] but remains <40% for advanced-stage or very high–risk disease.[10,15]

Recently, we demonstrated that the survival probability increased over time after radiotherapy in a risk-dependent manner among early-stage ENKTCL patients.[18] Annual hazard of death decreased to 5-6% at 3 years after completion of radiotherapy, irrespective of patient's initial risk category. Patients achieving progression-free disease within 24 months (PFS24) after current treatments had a 5-year OS rate of 92.2%, which was only slightly lower than the 94.3% in a matched general Chinese population.[19] In addition, despite the generally poor prognosis of elderly patients with early-stage ENKTCL,[20,21] elderly low-risk patients and a subgroup of high-risk patients who achieved PFS24 after radiotherapy have survival equivalent to that of the age- and sex-matched general population.[22] Given the variety of primary sites and the heterogeneity of clinical features and prognoses, it is necessary to know whether ENKTCL can be considered a curable disease in the modern treatment era. Although cure at the individual level is difficult to determine, statistical cure at the population level - i.e., no excess disease-related death from the primary disease or secondary complications—can be demonstrated by showing plateauing of the relative survival (RS) function.[23] By this method, colon cancer,[24] liver cancer,[25] and Hodgkin lymphoma,[26,27] have all been shown to be curable, but diffuse large B-cell lymphoma (DLBCL) might not be curable.[28,29,30] The curability of ENKTCL in the modern treatment era has not been investigated yet. In this study, we used the data of a large cohort of ENKTCL patients from the China Lymphoma Collaborative Group (CLCG) database to estimate the cure fraction and the survival of uncured patents in the entire cohort and in risk-stratified subgroups, and evaluate the association between OS and cure fraction.

Methods

Eligibility criteria and study population

We performed a retrospective analysis of the data of patients with newly diagnosed ENKTCL registered in the CLCG database between 2008 and 2016. Patients were eligible for inclusion in this study if they had received non-ANT-based chemotherapy and/or radiotherapy. Patients treated with unknown or ANT-based chemotherapy regimens were excluded. A total of 1,955 patients who met these criteria constituted the study population. This study was approved by the Institutional Review Boards; the need for informed consent was waived because only de-identified patient data were used.

Staging, risk stratification and definition

Pretreatment staging evaluations included physical examination; endoscopy of the upper aerodigestive tract; computed tomography (CT) scans of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) of the head and neck; bone marrow examination. Positron emission tomography (PET)/CT with 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) has been routinely used for staging since 2010. Patients were staged using the Ann Arbor staging system and were classified into low-, intermediate/low-, intermediate/high-, high-, and very high-risk groups according to the nomogram-revised risk index (NRI).[15] Definitions of primary site and primary tumor invasion (PTI) are provided in the *Online Supplementary Appendix*.

Treatment

Of the 1,123 patients with stage I disease, 691 (61.5%) received combined-modality therapy (CMT) of radiotherapy and chemotherapy, 305 (27.2%) received radiotherapy (RT) alone, and 127 (11.3%) received chemotherapy alone; Of the 599 stage II patients, 465 (77.6%) received CMT, 57 (9.5%) received RT alone, and 77 (12.9%) received chemotherapy alone; of the 233 stage III-IV patients, 146 (62.7%) received chemotherapy alone, and 87 (37.3%) received CMT. Details on chemotherapy regimens (*Online Supplementary Table S1*) and radiotherapy are provided in the *Online Supplementary Appendix*.

Statistical Methods

Outcome measure

OS was calculated from the date of initial treatment to the date of death or last contact and analyzed using the Kaplan–Meier method. RS was calculated as the ratio of the actual survival to the expected survival in an age-, sex-, and calendar year–matched general Chinese population (*Online Supplementary Appendix*) using the Ederer II method.[31] If visual examination showed plateauing of the RS curve, then cure was hypothesized to be plausible.

Cure model

Statistical cure is assumed to be achieved when surviving patients experience the same mortality as the general population. This concept applies at the group level and is

distinct from "medical cure" at the individual level. Cure fraction was defined as the level at which the RS curve reached a plateau.[32] Using a non-mixture cure model, the cure fraction was modeled with a logit link, whereas the RS of the uncured (fatal) group was assumed to follow a Weibull distribution. Details are provided in the *Online Supplementary Appendix*.

All statistical tests were two-sided, with type I error set at 5%. The OS rates were estimated and compared using the log-rank test in R 4.1.0 (http://www.r-project.org/). The cure models were fitted using the algorithms *strsmix* and *strsnmix* in STATA/SE 13.0 (STATA, College Station, TX, USA).[32] Linear regression analysis was used to assess the relationship between OS and cure fraction.

Results

Baseline clinical characteristics, initial response and overall survival

Table 1 lists the baseline clinical characteristics of the patients. The median age was 43 years (range, 1-87 years). Most patients had early-stage disease (88.1%), good performance status (PS; Eastern Cooperative Oncology Group [ECOG] score 0-1, 93.5%), and primary UADT site (93.6%). Elevated lactate dehydrogenase (LDH) was present in 533 (27.3%) patients, and PTI in 1,087 (55.6%) patients.

There were 1,833 patients who completed the response evaluation after the initial treatment. The complete response (CR), partial response (PR), stable disease (SD),

Table 1. Univariate analysis of cure fraction by clinical characteristics and risk stratification for extranodal nasal-type NK/T-cell lymphoma.

Variable	N (%)	Cure fraction (95% CI)	*P* for cure comparison
Sex			0.386
Male	1,381 (70.6)	71.3 (68.1-74.3)	
Female	574 (29.4)	73.8 (69.1-77.9)	
Stage			<0.001
I	1,123 (57.4)	78.5 (75.0-81.6)	
II	599 (30.6)	68.7 (63.9-73.1)	
III-IV	233 (11.9)	45.5 (35.5-55.9)	
Elevated LDH			<0.001
No	1,442 (72.7)	77.6 (74.8-80.2)	
Yes	533 (27.3)	58.0 (52.4-63.4)	
Age in years			0.518
<60	1,667 (85.3)	72.2 (69.4-74.8)	
>60	288 (14.7)	74.6 (67.4-80.8)	
B symptoms			0.001
No	1,184 (60.6)	75.5 (72.2-78.5)	
Yes	771 (39.4)	66.4 (61.6-70.9)	
ECOG score			<0.001
0-1	1,827 (93.5)	74.4 (71.7-77.0)	
≥2	128 (6.5)	38.3 (28.8-48.8)	
PTI			<0.001
No	868 (44.4)	78.4 (74.3-82.0)	
Yes	1087 (55.6)	67.1 (63.7-70.4)	
Primary site			0.033
UADT	1,829 (93.6)	73.6 (71.0-76.1)	
Extra-UADT	126 (6.4)	34.9 (14.1-63.6)	
NRI			<0.001
Low risk	438 (22.4)	87.1 (82.4-90.8)	
Int-low risk	564 (28.8)	77.8 (73.0-81.9)	
Int-high risk	517 (26.4)	65.5 (59.1-71.4)	
High risk	277 (14.2)	60.4 (53.4-67.1)	
Very high risk	159 (8.1)	44.3 (34.3-54.6)	

ECOG: Eastern Cooperative Oncology Group; Int: intermediate; LDH: lactate dehydrogenase; NRI: nomogram-revised risk index; UADT: upper aerodigestive tract; PTI: primary tumor invasion; Int-low: intermediate-low; Int-high: intermediate-high.

and progression disease (PD) rates after initial treatment were 70.1%, 18.6%, 1.9%, and 9.4% for the whole cohort, with 73.3%, 18.4%, 1.6% and 6.7% for early-stage disease, and 45.1%, 19.9%, 3.9% and 31.1% for advanced-stage disease, respectively.

The 5-year and 10-year OS rates for the entire cohort were 71.2% (95% CI: 68.9-73.5) and 63.8% (95% CI: 56.9-68.3), respectively.

Relative survival

The 5-year and 10-year RS rates for the entire cohort were 73.5% (95% CI: 71.1-75.9) and 69.0% (95% CI: 64.5-73.8), respectively (*Online Supplementary Figure S1A*). In the whole cohort, as well as in most subgroups stratified by clinical factors and NRI, the RS curves reached a clear plateau within 5 years of diagnosis (*Online Supplementary Figure S2A-H*), indicating the statistical plausibility of cure for ENKTCL.

Cure fraction and prognostic factors

The cure model converged and fitted well for ENKTCL in the entire cohort and in each subgroup. The cure fraction of the entire cohort was 71.9% (95% CI: 69.3-74.5), but the predicted RS of uncured patients was poor, with the median survival of only 1.1 years (95% CI: 1.0-1.3) (Figure 1A). The excess hazard rate in the entire cohort was 15.6% in the first year and then decreased continuously. The cure time, which was defined as the time at which 95% of the “uncured" patients would have died, was 4.5 (95% CI: 3.7-5.5) years after treatment. Thus, beyond 4.5 years, excess mortality attributed to ENKTCL became statistically negligible; that is, mortality of ENKTCL patients approximated that of the general population. In contrast, the excess hazard of death for uncured patients increased steeply in the first year to approximately 66% and then progressively increased over time (Figure 1B). In order to assess the potential influence of the inclusion of children and adolescent patients (whole cohort *vs*. cohort of patients ≥20 years old) on cure fraction, additional sensitivity analysis was conducted. The cure fraction of 72.1% (95% CI: 69.5-74.7) for patients ≥20 years old (n=1,855) was very close to that of 71.9% (95% CI: 69.3-74.5) for all patients with inclusion of children and adolescent (*Online Supplementary Figure S3*). As shown in *Online Supplementary Figure S3*, the relative survival curves for the two cohorts almost overlapped.

Cure fractions stratified by clinical features are presented in Table 1. In univariate analysis, the factors significantly associated with high cure probability were no B symptoms, stage I disease, ECOG score 0-1, normal LDH, absent PTI, and primary UADT site (all $P<0.05$ by the cure model test; Figure 2A-F). Although patients over 60 years had significantly worse OS than patients younger than 60 years ($P=0.002$ by log-rank test; *data not shown*), there was no significant difference in the cure fraction between the two age-groups after adjusting for background mortality ($P= 0.518$ by the cure model test).

The median survival time of uncured patients ranged from 0.6 to 2.1 years in different subgroups (*Online Supplementary Table S5*). Cure time was attained within 5 years in almost all subgroups, except for the subgroup of extra-UADT disease. These results indicated that patients achieving a 5-year survival could be considered statistically cured.

Cure fraction in nomogram-revised risk index-defined risk groups

We examined whether the NRI could discriminate the cure fractions. According to the NRI, the cure fractions for the

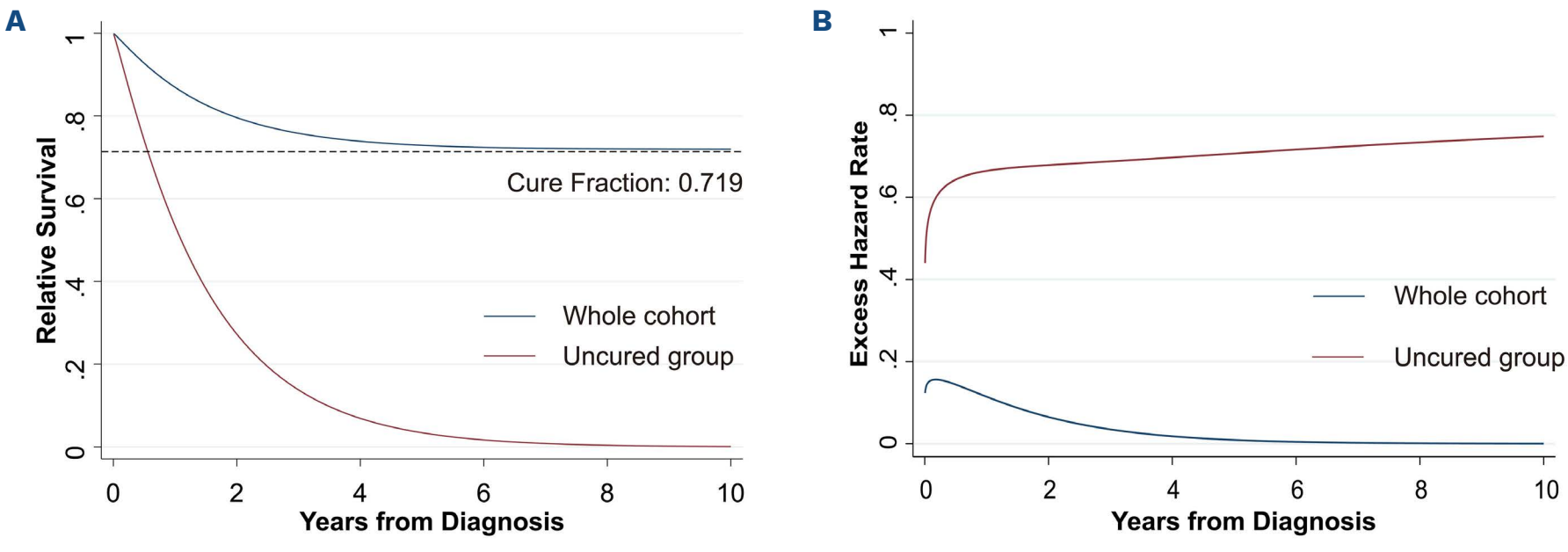

Figure 1. Cure model results. (A) Predicted relative survival curves of the whole cohort of patients (blue line) and the uncured patients (red line) using the non-mixture cure model. In the entire group, from 4.5 years after treatment onward, the survival plateaued at approximately 72%, which represents the cure fraction (dashed line). (B) Excess hazard rate of the whole cohort (blue line) and the uncured patients (red line). In the whole cohort, the excess hazard continued to decrease until it approached zero at 4.5 years after treatment. Conversely, in uncured patients, the excess hazard progressively increased over time.

low-, intermediate/low-, intermediate/high-, high-, and very high–risk subgroups were 87.1% (95% CI: 82.4-90.8), 77.8% (95% CI: 73.0-81.9), 65.5% (95% CI: 59.1-71.4), 60.4% (95% CI: 53.4-67.1), and 44.3% (95% CI: 34.3-54.6; *P*<0.001 by the cure model test; Figure 3A). The median survival time of uncured patients decreased as NRI risk factors increased, ranging from 1.6 years for low-risk patients to 0.6 years for very high–risk patients (Figure 3B). Cure time was attained within 5 years across all risk groups (*Online Supplementary Table S5*).

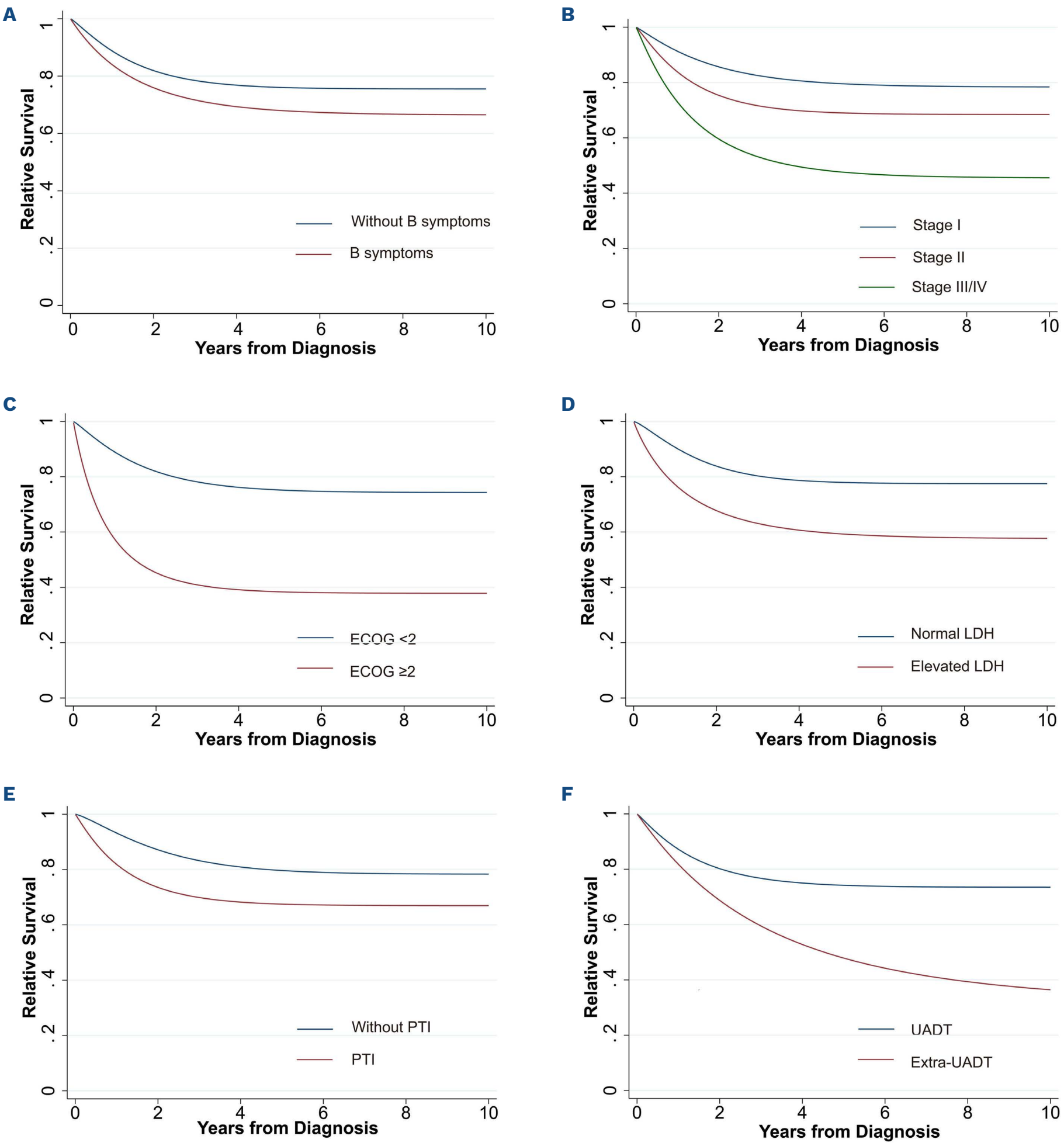

Figure 2. Predicted relative survival curves by prognostic factor. Relative survival calculated using non-mixture cure model by (A) B symptoms, (B) stage; (C) Eastern Cooperative Oncology Group (ECOG) score; (D) lactate dehydrogenase (LDH), (E) primary tumor invasion (PTI), and (F) primary upper aerodigestive tract (UADT) site.

Association between overall survival and cure fraction

As cure time was attained within 5 years across almost all subgroups, we explored whether the 5-year OS rate could be a good proxy for cure fraction. The 2- to 5-year OS correlated well with cure fraction across subgroups stratified by clinical factors and NRI-defined risk groups (Figure 4; all $P<0.001$). Moreover, the OS rates at 4 years (determination coefficient, $R^2=0.96$; $P<0.001$) and 5 years ($R^2=0.94$; $P<0.001$) were very close to the estimated cure fraction (Figure 4C, D). Thus, the 5-year OS rate can be proposed as a surrogate for cure fraction in ENKTCL patients.

Discussion

In this large comprehensive study, we established that despite the aggressive and heterogeneous clinical behavior of ENKTCL, the notion of cure is applicable and robust, irrespective of clinical features and risk stratification. Across subgroups of ENKTCL patients, statistical cure is achievable with current treatment strategies. Cure fractions were associated with clinical prognostic factors (e.g., B symptoms, stage, PS, PTI, LDH, and primary UADT site). However, old age was not significantly associated with cure fraction after adjusting for background mortality. Moreover, the 5-year OS rate was found to be a valid surrogate for cure fraction in ENKTCL patients. The findings of this study can help in improving clinical practice and in designing clinical trials on this particular lymphoma.

To the best of our knowledge, this is the first study to quantitatively evaluate the statistical curability of ENKTCL treated with current methods. In contrast to traditional survival analysis, where the assumption is that all patients are at risk of disease-related death, the cure model allows for characterization of the heterogeneity in the plateau areas of survival plots by splitting patients into those who are cured (i.e., those with the same mortality hazard as the general population) and those who are not (i.e., those with higher mortality hazard than the general population). Using the non-mixture cure model with incorporation of background mortality, we demonstrated that the overall probability of statistical cure was approximetely 72% in ENKTCL patients treated with current methods. Despite the heterogeneity of the disease and its aggressive clinical behavior, the RS curves plateaued and the cure model converged and fitted well across most subsets. Thus, from a statistical standpoint, a population-based cure is plausible and robust for ENKTCL. This phenomenon is consistent with our previous findings and those of others that, despite an aggressive disease course in the first few years, late relapse is rare in ENKTCL beyond 5 years.[12,18,19,33] Cure fraction is also high and stable for young and middle-aged Hodgkin lymphoma patients treated primarily with chemotherapy.[26,27] However, similar cure is not attained for DLBCL in the modern immunochemotherapy era; some DLBCL patients manifest a pattern of continued late relapse, without flattening of survival curves.[28,29,30] These distinct disease courses may be attributed to underlying differences in biological behavior and treatment principles.

Interestingly, the significant determinants of chance of cure (PS, PTI, LDH, and stage) that were identified in this study mirrored covariates in the previously established NRI: PTI, LDH, and stage reflect tumor burden; stage and PTI reflect invasive potential; and PS reflects the patient's ability to tolerate treatment.[14,15] Meanwhile, despite being a proven independent adverse factor for OS in ENKTCL[14-16] and DLBCL,[34] age >60 years was not significantly associated with cure fraction after adjusting for background

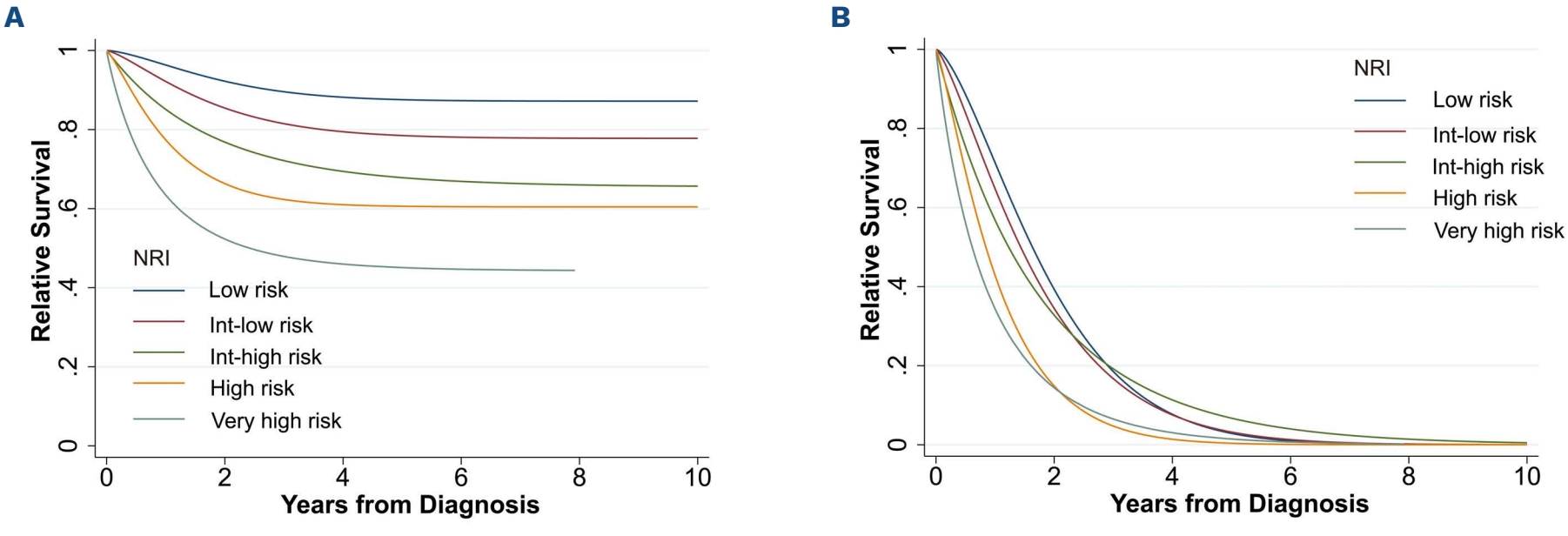

Figure 3. Cure model results by risk-stratified groups. Predicted relative survival of each nomogram-revised risk index (NRI)-defined subgroup of patients (A) and of the uncured patients in each NRI-defined subgroup (B). Int-low: intermediate-low; Int-high, intermediate-high.

mortality in ENKTCL. In our previous study, elderly low-risk ENKTCL patients and a subgroup of high-risk patients who achieved PFS24 had survival equivalent to that of the matched general population.[22] In this study, we further show that elderly ENKTCL patients have as good a chance of cure as young patients. In contrast, in other hematologic malignancies, such as acute myeloid leukemia,[35] Hodgkin lymphoma,[26,27] and DLBCL,[28] where intensified chemotherapy is used with the aim of achieving cure, elderly patients usually have lower cure fractions than younger patients. One possible explanation is that elderly patients are less able to complete first-line intensified systemic treatment due to comorbidities and greater susceptibility to treatment side effects. However, radiotherapy, which is well tolerated by the elderly,[22] is the backbone of first-line treatment for early-stage ENKTCL patients.[4-8,21]

Although the NRI system was derived from the Cox proportional hazards model with the primary endpoint of OS,[15] it performed well in predicting and discriminating the cure fraction. The NRI system stratified ENKTCL patients into five subgroups, ranging from a low-risk subset (with highly curability of 87%) to a very high–risk subset (with poor curability of 44%). The NRI system can be used for classifying patients according to possibility of cure and selecting first-line treatment and follow-up strategy.[7,17,18] Use of the NRI system by researchers across countries would facilitate international multicenter clinical trial design and comparison of results.

The uncured (fatal) ENKTCL patients had notably poor

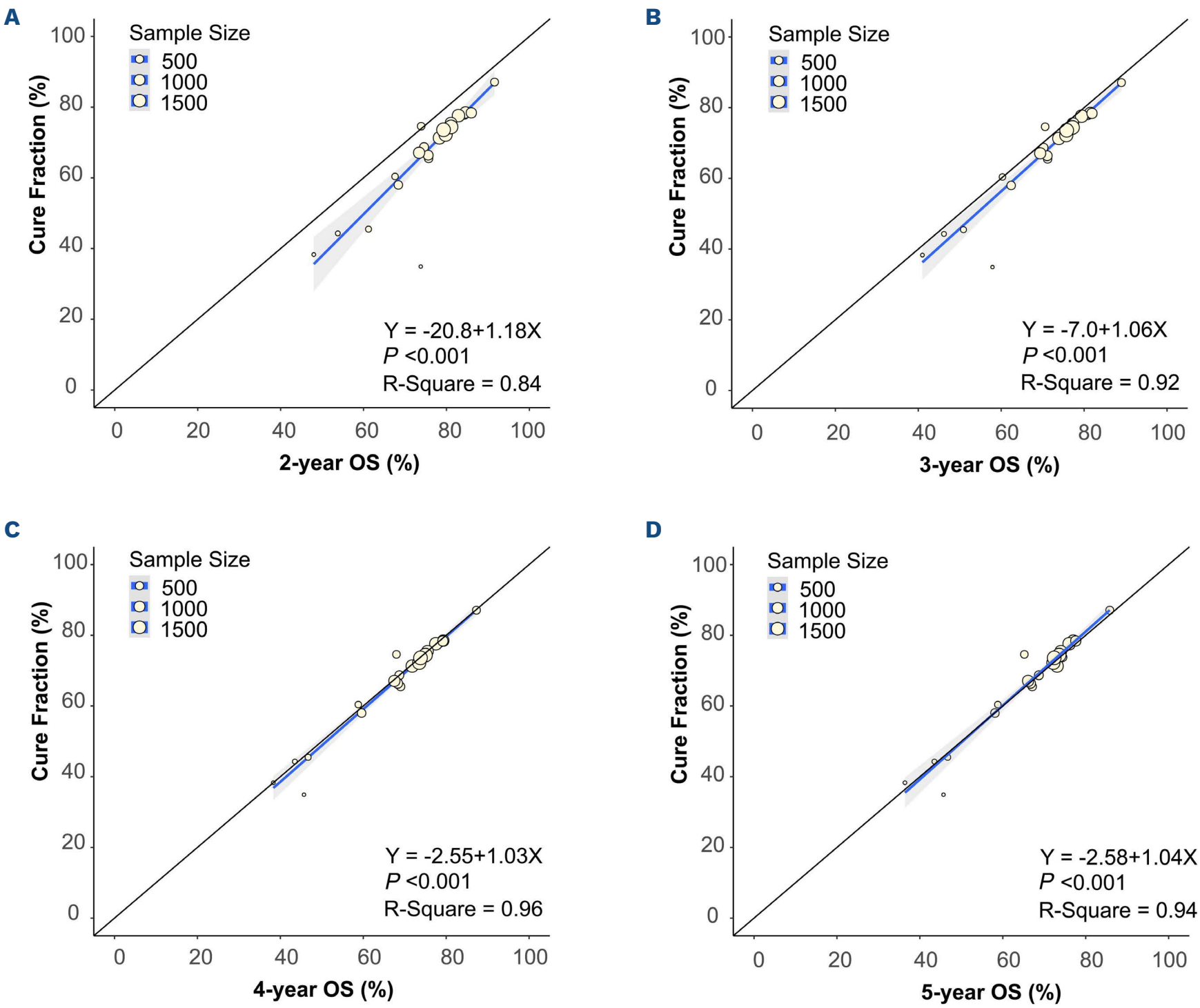

Figure 4. Association of overall survival and cure fraction by prognostic factors and nomogram-revised risk index-defined risk groups. The (A) 2-year, (B) 3-year, (C) 4-year, and (D) 5-year overall survival (OS) by subgroups were linearly associated with the corresponding cure fraction. The 3-year, 4-year, and 5-year OS estimations were very close to the cure fraction estimation. *R-square*: determination coefficient.

prognosis, with median survival time of 1.1 years (0.6 to 1.6 years in very high–risk to low-risk groups). This is consistent with the aggressive disease course of the uncured DLBCL patients, with median survival times from 0.6 to 1.9 years in high- to low-risk groups.[28] In contrast, the uncured young and middle-aged Hodgkin lymphoma patients had a relatively favorable survival (median, 4.6 years).[26] Therefore, the uncured patients with different types of lymphomas manifested apparently heterogeneous clinical courses.

Cure time is an important factor to be considered during follow-up of patients. Traditionally, achievement of 5-year survival has been the surrogate for "cure" in many cancers, but this is only based on experience and not on evidence. In this study, we show that survival for 5 years establishes cure for ENKTCL patients from a statistical standpoint; the mortality of survivors approximated that of the general population at 4.5 years after current treatment. The 5-year OS estimates were very close to the corresponding cure fractions across subgroups, indicating that 5-year OS was a good surrogate for the cure fraction. This finding provides patient, clinicians, and statisticians with a valuable time point. For patients, once they reach the 5-year mark, they can be reassured that their risk of death is very close to that of the general population. For clinicians, the 5-year mark is a milestone after which further reduction of follow-up frequency might be appropriate. For statisticians, during prospective trials design, there might be little value in defining late recurrence or disease-related death as endpoints beyond 5 years; instead, quality of life, treatment-related adverse effects, or secondary cancers, might be more relevant during further follow-up.

Strengths of this study included that our study was based on a large multicenter cohort, with high-quality data and sufficiently long follow-up. Data based on patients treated outside of clinical trials provide real-world benchmark estimates of prognosis for extrapolation to the general population. Moreover, the cure model based on RS data is suited for quantifying long-term survival and has the advantage of not relying on accurate reporting of causes of death. However, there were several limitations in this study. Firstly, as patients with extra-UADT disease have more aggressive clinical course and lower cure fraction, it remains unclear whether these patients should be treated differently than patients with UADT disease. Secondly, we recognize that patients from the endemic area (China) in the current study tended to have favorable prognostic features (e.g., younger ages and early stages) than those in non-endemic areas (Europe and North America). In order to justify this skewing, the cure fractions were assessed according to stage and age. Despite of this, additional studies are still required to investigate the cure fraction in patients from non-endemic areas. Thirdly, we acknowledge that the imaging modality information (patients who underwent PET/CT scan) was not available for each patient in the CLCG database. Fifteen percent of patients in this study were diagnosed before 2010 when PET/CT scan was not routinely used for staging. PET/CT scan might upstage some cases, as it is more sensitive than CT in identifying small distant extranodal disease in lymphoma.

In conclusion, this study establishes the robustness of the notion of cure and the varied cure probability in ENKTCL from a population-based standpoint in the modern treatment era. Patients who succumb to ENKTCL within 5 years comprise a very special subset of patients with properties that are yet to be described. The use of biological markers of cure at the individual level needs to be examined in future studies.

Disclosure

No conflicts of interest to disclose.

Contributions

S-NQ and YXL designed the research. YXL, SNQ, XL, and LLZ collected and analyzed data. XL, LLZ, SNQ, and YXL wrote the paper. All authors provided patients data and approved the paper.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding authors (S-NQ) on reasonable request.

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