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Research article

Optimizing the prognostic capacity of baseline ^{18}F-FDG PET/CT metabolic parameters in extranodal natural killer/T-cell lymphoma by using relative and absolute thresholds

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ABSTRACT

Objectives: To investigate the prognostic capacity of baseline ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) metabolic parameters in extranodal natural killer/T-cell lymphoma (ENKTCL), and the influence of relative thresholds (RT) and absolute thresholds (AT) selection on prognostic capacity.

Materials and methods: Metabolic tumor volume (MTV)-based parameters were defined using RTs (41 % or 25 % of maximum standardized uptake value [SUVmax]), ATs (SUV 2.5, 3.0, 4.0, or mean liver uptake) in 133 patients. Metabolic parameters were classified into avidity-related parameters (SUVmax, mean SUV [SUVmean], standard deviation of SUV [SUVsd]), volume-related parameters (RT-MTV), and avidity- and volume-related parameters (total lesion glycolysis [TLG] and AT-MTV). The prognostic capacity of the metabolic parameters and the effects of different threshold types (RT vs. AT) were evaluated.

Results: All metabolic parameters were moderately associated with prognosis. However, the area under the receiver operating characteristic curve of MTV and TLG was slightly higher than that of avidity-related parameters for predicting 5-year progression-free survival (PFS) (0.614–0.705 vs. 0.563–0.609) and overall survival (OS) (0.670–0.748 vs. 0.562–0.593). Correlations of MTV and avidity-related parameters differed between RTs ($r < 0.06$, $P = 0.324$–0.985) and ATs (r 0.56–0.84, $P \leq 0.001$). AT-MTV was the optimal predictor for PFS and OS, while RT-TLG was the optimal predictor for PFS, and the combination of RT-MTV with SUVmax was the optimal predictor for OS.

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Conclusion: The incorporation of volume and avidity significantly improved the prognostic capacity of PET in ENKTCL. Composite parameters that encompassed both avidity and volume were recommended.

Abbreviations

ENKTCL	extranodal natural killer/T-cell lymphoma
UADT	upper aerodigestive tract
OS	overall survival
PET	positron emission tomography
DLBCL	diffuse large B-cell lymphoma
FDG	fluorodeoxyglucose
SUV	standardized uptake value
SUVmax	maximum standardized uptake value
MTV	metabolic tumor volume
TLG	total lesion glycolysis
CTV	clinical tumor volume
RTs	relative thresholds
ATs	absolute thresholds
SUVmean	mean standardized uptake value
EFA	exploratory factor analysis
LASSO	least absolute shrinkage and selection operator
MRI	magnetic resonance imaging
EANM	European Association of Nuclear Medicine
NRI	nomogram revised-risk index
PERCIST	PET Response Criteria in Solid Tumors
SUVsd	standard deviation of standardized uptake value
PFS	progression-free survival
ROC	receiver operating characteristic
AUC	area under the curve
HR	hazard ratio
CI	confidence interval

1. Introduction

Extranodal natural killer/T-cell lymphoma (ENKTCL), with an aggressive and heterogeneous clinical behavior, is the most common subtype of peripheral T-cell lymphoma in China [1]. It usually involves upper aerodigestive tract (UADT) structures such as the nasal cavity and Waldeyer ring [2]. The nomogram-revised risk index (NRI) with incorporation of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor invasion (PTI), lactate dehydrogenase (LDH) and Ann Arbor stage demonstrated good capability in predicting prognosis and guiding treatment decisions for patients with ENKTCL [3,4]. Treatment strategies combining asparaginase-based chemotherapy and upfront radiotherapy have been shown to improve long-term outcomes in patients with ENKTCL [5], yielding 5-year overall survival (OS) and cure fraction rates of approximately 70 % [6].

Over the last two decades, positron emission tomography (PET) has become an integral and crucial part of the diagnosis and management of lymphomas, particularly in diffuse large B-cell lymphoma (DLBCL) [7]. For ENKTCL, as an fluorodeoxyglucose (FDG)-avid aggressive lymphoma, PET also plays an important role in initial staging [8] and predicting the prognosis [9]. An meta-analysis has demonstrated that baseline maximum standardized uptake value (SUVmax) was an independent prognostic factor in ENKTCL [9], while a few studies suggested that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) showed good predictive values for survival [10,11]. Due to the rarity of ENKTCL, most studies evaluating prognosis of baseline PET metabolic parameters had small sample sizes and arbitrarily selected metabolic parameters, making it challenging to draw valuable conclusions in clinical application [9].

Recommendations based on the Deauville score and Lugano classification have standardized the interpretation of SUVmax and directly affected the management and outcome of lymphoma patients [7]. In comparison with SUVmax, volumetric parameters such as MTV and TLG show better prognostic performance in malignancies [12,13]. MTV, defined as the volume of increased ^{18}F-FDG uptake within the clinical tumor volume (CTV), can better reflect the malignancy and tumor burden compared to CTV. However, wider clinical implementation of MTV is limited due to the lack of uniform thresholds to define it [14]. In lymphomas, relative thresholds (RTs) (such as 41 % or 25 % of the SUVmax), absolute thresholds (ATs) (such as SUV 2.5–4.0) [9,14], or physiological liver metabolism

[15] were usually used to assess MTV and predict prognosis. The use of metabolic parameters according to the different thresholds varied between studies, leading to inconsistent results [14]. For example, when using ATs, AT-MTV other than AT-TLG was an independent predictor of survival [16,17]. In contrast, when using RTs, RT-TLG other than RT-MTV was an independent predictor of survival [18,19]. It is unknown whether the different results were related to the different threshold types or lymphoma types. Furthermore, because of the use of different MTV thresholds, it was difficult to make a definitive conclusion of optimal metabolic parameters [12,13]. Therefore, it is urgent to clarify the differences of threshold types and optimize metabolic parameters in lymphomas.

Because of the interactions among metabolic parameters, multivariate Cox regression analysis may yield less reliable statistical inferences, leading to the difficulty in optimizing the metabolic parameters. Previous studies mainly focused on the effect of thresholds on MTV, without consideration of the effect of MTV changes on parameters such as TLG and mean SUV (SUVmean) [20–22]. Exploratory factor analysis (EFA) [23] and least absolute shrinkage and selection operator (LASSO) [24] evaluations may help identify the optimal metabolic parameters. Given the potential prognostic value of metabolic parameters in patients with ENKTCL, optimization of metabolic parameters with advanced statistical methods is worth consideration. This study aimed to evaluate the effect of different metabolic parameters on prognosis in ENKTCL and explore the influence of different type of thresholds (RTs and ATs) on prognostic capacity.

2. Materials and methods

2.1. Eligibility and study population

This was a retrospective study. Eligibility criteria for this study were: (1) patients with newly-diagnosed ENKTCL between September 2009 and January 2020 in a registry database in our institution, (2) primary disease located in the UADT, and (3) ^{18}F-FDG PET/CT data available before treatment within one month, and (4) visible primary tumor on PET/CT and magnetic resonance imaging (MRI). Finally, 133 eligible patients were enrolled. ^{18}F-FDG PET/CT acquisition was performed at baseline and conducted in accordance with the European Association of Nuclear Medicine (EANM) guidelines [25]. The study was conducted in accordance with the precepts of the Helsinki declaration and received approval from our Institutional Review Board. Patient consent was waived by our Institutional Review Board due to the retrospective nature of this study.

All patients were staged according to Ann Arbor staging system and stratified by the NRI model [3,4]. Patients with early-stage ENKTCL received radiotherapy with (n = 77) or without (n = 45) chemotherapy, while only two patients received chemotherapy alone. Patients with advanced-stage disease received systemic chemotherapy (n = 9). Chemotherapy consisted of non-anthracycline-based regimens.

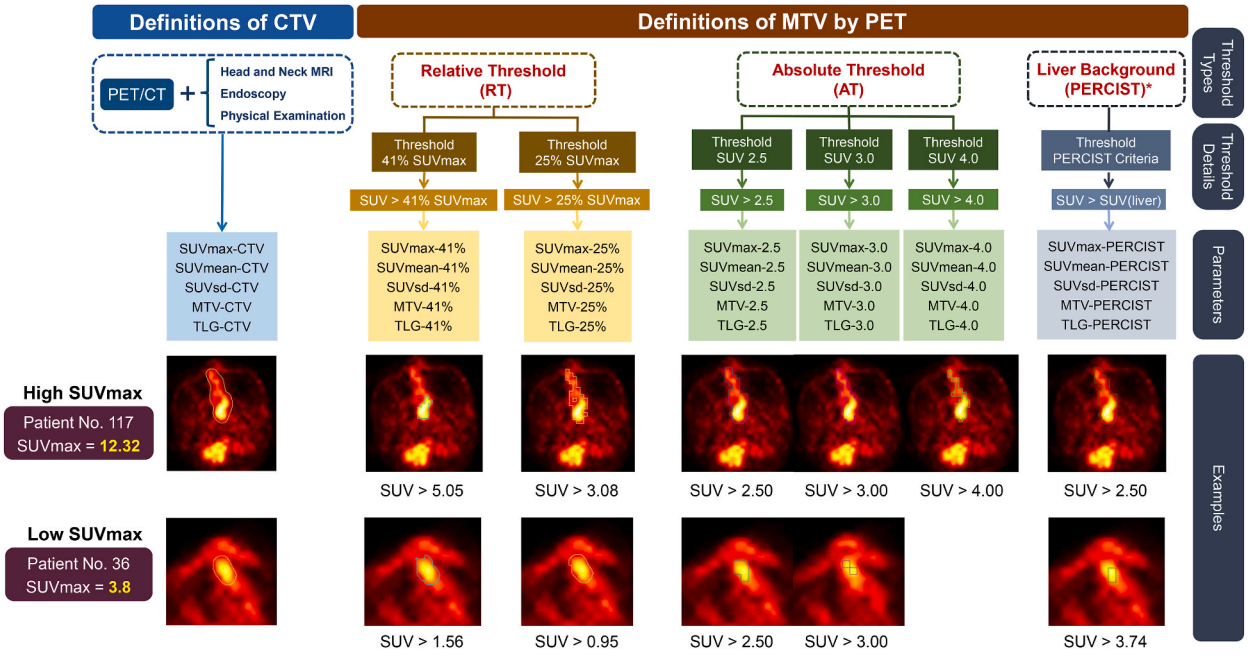

Fig. 1. Diagram of the research proposal. MTV was measured using RTs (41 %SUVmax and 25 %SUVmax), ATs (SUV 2.5, SUV 3.0 and SUV 4.0) and the PERCIST criteria within the CTV of each patient. *PERCIST criteria: SUV > mean liver uptake (1.5 × liver mean + 2 × standard deviation).

2.2. ^{18}F-FDG PET/CT imaging

The detailed protocol for acquisition of PET/CT images is presented in Supplemental Material 1. All images were reviewed by two physicians using imaging software MIM 7.4.1 (MIM Software Inc., Cleveland, OH, USA). CTVs were manually delineated on PET/CT images combined with registration of MRI and reference endoscopy and physical examination findings; this process was jointly performed by two radiation oncologists. In addition, high metabolic subregions were measured using the following thresholds within CTV (Fig. 1): (1) RT of 41 % SUVmax (SUV >41 % SUVmax); (2) RT of 25 % SUVmax (SUV >25 % SUVmax); (3) AT of SUV 2.5 (SUV >2.5); (4) AT of SUV 3.0 (SUV >3.0); (5) AT of SUV 4.0 (SUV >4.0); and (6) PET Response Criteria in Solid Tumors (PERCIST) threshold (SUV > mean liver uptake [1.5 × liver mean + 2 × standard deviation]).

The SUVmax was the voxel-wise maximum SUV within the respective MTV and normalized to lean body mass using the Janmahasatian formula [26]. The SUVmean was the mean SUV within the respective MTV. TLG was calculated as MTV × SUVmean. Standard deviation of SUV (SUVsd) was defined within the respective MTV. All metabolic parameters were measured for primary tumor lesions. Logical rules were made to distinguish parameters with different thresholds. Briefly, the name was composed of the parameter as the prefix and the abbreviation of threshold as the suffix, separated by "-" (Fig. 1 and Supplemental material 2).

2.3. Endpoint and statistical analysis

Progression-free survival (PFS) was defined as the time from the start of the first treatment to progression, relapse, or death from any cause. OS was defined as the time from the start of the first treatment to death from any cause. Spearman correlation test was conducted, and the correlation coefficients were denoted as *r*. EFA involving principal-axis factoring with an orthogonal rotation was conducted to identify patterns of metabolic parameters with different thresholds. Parallel analysis was used and confirmed by scree plot to determine the number of factors to extract. The optimal cut-off values of each metabolic parameter for 5-year PFS and OS rates were determined by receiver-operating characteristics (ROC) curve. Furthermore, area under the curve (AUC) of different metabolic parameters were used to compare survival differences by multi-comparison Delong's test. Kaplan–Meier curves and log-rank tests were used to investigate the differences in survival between groups. The adjusted survival curves, p value, with hazard ratio (HR) and 95 %

Table 1
Clinical features of enrolled ENKTCL patients.

	Patients	
Characteristics	No.	%
All	133	100
Age		
≤60	113	85.0
>60	20	15.0
Gender		
Male	99	74.4
Female	34	25.6
ECOG		
0-1	127	95.5
≥2	6	4.5
B Symptom		
No	78	58.6
Yes	55	41.4
LDH		
Normal	98	73.7
Elevated	35	26.3
PTI		
No	27	20.3
Yes	106	79.7
Ann Arbor		
I	64	48.1
II	60	45.1
III/IV	9	6.8
NRI risk group		
Low risk	20	15.0
Intermediate risk	76	57.1
High risk	28	21.1
Very high risk	9	6.8
Treatment		
Early-stage patients		
Radiotherapy	45	33.8
Radiotherapy combined with chemotherapy	77	57.9
Chemotherapy	2	1.5
Advanced-stage patients		
Chemotherapy	9	6.8

confidence interval (CI) were calculated based on multivariate Cox proportional hazards regression. LASSO was used to select optimal parameters, and 10-fold cross-validation with a minimum criterion was applied. The concordance index (C-index) was used to assess the discriminative ability of optimal metabolic parameters for PFS and OS. A two-tailed p value of ≤0.05 was considered significantly different. Statistical analyses were performed using the *compareGroups, corrplot, psych, ggplot2, survival, survminer,* and *glmnet* packages in R version 4.1.1 (https://www.r-project.org/).

3. Results

3.1. Clinical features and survival

The clinical features are summarized in Table 1. The median patient age was 44 years. 124 patients (93.2 %) had early-stage disease and 9 patients had advanced-stage disease. According to stage-adjusted NRI, 15 % of patients were classified in the low-risk group, whereas 85 % were in intermediate- and high-risk groups. Over a median follow-up of 64 months, 5-year PFS and OS rates for the whole group were 66.4 % and 76.9 %, respectively.

3.2. Distributions of different thresholds and metabolic parameters

The distributions of different thresholds were shown in Fig. S1. The PERCIST threshold was relatively concentrated in comparison with the RTs, and its correlation with the SUVmax was negligible ($R^2 = 0.043$). Therefore, we suggested the PERCIST threshold as the AT in this study. The results of metabolic parameters were described in detail (Table S1).

3.3. Classification of the metabolic parameters with different thresholds

To make clear, we classified the metabolic parameters with different threshold. Except RT-MTV and AT-MTV, which showed weak-to-moderate correlations ($r = 0.46$–0.65), strong internal correlations were observed between different thresholds for the same parameters (all $r \geq 0.86$; Fig. 2A). SUVmean and SUVsd were classified as avidity-related parameters because of their strong correlation with SUVmax (all r ≥ 0.91 and $P \leq 0.001$) but no relevance to RT-MTV ($r < 0.06$ and $P = 0.324$–0.985; Fig. 2A). The correlations of the three avidity-related parameters (SUVmax, SUVmean and SUVsd) with MTV were distinct between RTs and ATs. Moderate-to-high correlations were observed between AT-MTV and the three avidity-related parameters (r 0.56–0.84, $P \leq 0.001$; Fig. 2A). In contrast, no significant correlations were found between RT-MTV and these avidity-related parameters ($r < 0.06$ and $P = 0.324$–0.985; Fig. 2A). Regardless of the thresholds, TLG exhibited a moderate-to-strong correlation with the three avidity-related parameters (r 0.50–0.88, $P \leq 0.001$; Fig. 2A). On the basis of these correlation analyses, AT-MTV and TLG were considered as both avidity- and volume-related parameters, while RT-MTV was recognized as volume-related parameter, but not an avidity-related parameter.

Given the intricate correlations of metabolic parameters, we conducted EFA to examine the underlying factor structure and validate

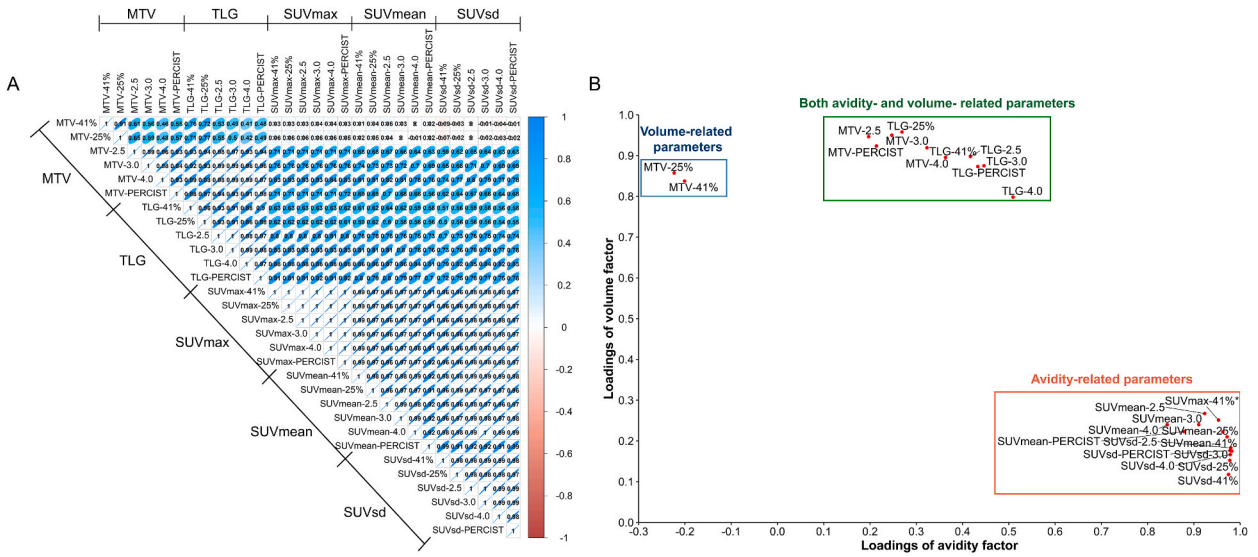

Fig. 2. Classification of metabolic parameters with different thresholds by correlation analysis and EFA. **(A)** Stronger positive correlations are indicated by darker blue and more elliptical shapes. A cross within a box indicates that the corresponding p-value for r was insignificant. **(B)** Metabolic parameters can be divided into three categories by EFA analysis. *SUVmax varied very slightly among different thresholds, so SUVmax-41 % was selected as a representative of SUVmax to be included in EFA. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the above classification drawn from the correlation analysis. In the scree plot, two latent factors explained 91.7 % of the total variance, which was the most parsimonious result (Fig. S2 and Table S2). On the basis of the loadings of each factor corresponding to each parameter, these two factors were roughly considered to represent avidity and volume, respectively. The two-factor structure can classify metabolic parameters with different thresholds into three categories: parameters related to avidity alone, represented by SUVmax, SUVmean and SUVsd; parameters related to volume alone, represented by RT-MTV; and avidity- and volume-related parameters, represented by TLG and AT-MTV. This is consistent with the observations from the correlation analysis (Fig. 2B).

3.4. Superior prognostic performance of MTV and TLG versus avidity-related parameters

First, we evaluated the effect of different metabolic parameters on prognosis. As shown in Table 2 and Fig. 3A and B, all metabolic parameters were moderately associated with prognosis, regardless of thresholds, with the AUCs for 5-year PFS and OS rates ranging from 0.562 to 0.748. However, the AUCs of three avidity-related parameters (SUVmax, SUVmean and SUVsd) for PFS and OS were lower than those of MTV and TLG (0.563–0.609 vs. 0.614–0.713 for PFS and 0.562–0.593 vs. 0.670–0.748 for OS, respectively). Thus, the prognostic performance of parameters related to volume alone and those related to both avidity and volume was better than that of parameters related to avidity alone. Moreover, significant differences in PFS and OS were observed among different thresholds for MTV ($P = 0.041$ for PFS and 0.017 for OS) and TLG ($P = 0.009$ for PFS and 0.031 for OS).

3.5. Interactions between MTV and avidity-related parameters with RTs and ATs

To compare the different effects of thresholds (RT vs. AT) on prognosis, we further investigated the different interactions of MTV and avidity-related parameters, specifically SUVmean and SUVmax, at different thresholds. The optimal cutoff values for each metabolic parameter were determined using ROC analysis for survival analysis (Table S1). After adjusting for NRI risk groups using multivariable analysis (Fig. S3A-L), significant differences were observed in PFS and OS between patients with low and high SUVmean ($P = 0.017$–0.050), except for SUVmean-PERCIST in PFS ($P = 0.124$). Moreover, after adjusting for both NRI and MTV (Fig. 4A-L), differences in PFS and OS were only observed between low and high RT-SUVmean (P = 0.006–0.033), but not between low and high AT-SUVmean ($P = 0.467$–0.880). Similar results were obtained for the association between MTV and SUVmax (Fig. S4A-L and Fig. 5A-L). This finding suggested a strong interaction between avidity-related parameters (SUVmean and SUVmax) and AT-MTV, but no interaction between avidity-related parameters and RT-MTV.

We also conducted a detailed analysis of SUV distribution within individual primary tumors of patients with ENKTCL. The results showed an asymmetric pattern in the distribution of SUVs within each tumor, characterized by long right-skewed tails (Fig. S5A) and positive skewness values (skewness >0; Fig. S5B). These results indicated a consistent right-skewed pattern in the distribution of SUV values within each tumor. As shown in Fig. 1, RT-MTV and AT-MTV refer to the high metabolic regions selected within CTV using their respective threshold values. RT is defined as a percentage of SUVmax (e.g., 41 % SUVmax, 25 % SUVmax), with the thresholds dynamically adjusted based on variations in SUVmax in ENKTCL patients. Due to the similar SUV value distribution within each tumor in ENKTCL, the size of the RT-MTV is less influenced by the magnitude of SUVmax. In contrast, AT is a type of fixed threshold independent of SUVmax (e.g., SUV 2.5, SUV 3.0, SUV 4.0) and remains constant across various SUVmax values. As a result, the size of AT-MTV, determined by fixed thresholds, is more sensitive to changes in the magnitude of SUVmax.

Table 2
Comparison of AUC for 5-year PFS and OS of baseline metabolic parameters with different thresholds.

Parameters	Thresholds of MTV						P[a]
	RT		AT				
	41 % SUVmax	25 % SUVmax	SUV 2.5	SUV 3.0	SUV 4.0	PERCIST	
5-year PFS							
Volume- and avidity-related parameters							
MTV	0.614[b]	0.635[b]	0.698	0.698	0.687	0.713	**0.041**
TLG	0.667	0.689	0.692	0.688	0.677	0.705	**0.009**
Avidity-related parameters only							
SUVmax	0.605	0.605	0.605	0.606	0.607	0.609	–
SUVmean	0.602	0.605	0.587	0.592	0.597	0.563	0.506
SUVsd	0.592	0.595	0.591	0.598	0.592	0.604	0.250
5-year OS							
Volume- and avidity-related parameters							
MTV	0.670[b]	0.705[b]	0.748	0.745	0.723	0.737	**0.017**
TLG	0.711	0.738	0.728	0.724	0.702	0.727	**0.031**
Avidity-related parameters only							
SUVmax	0.590	0.590	0.590	0.591	0.590	0.593	–
SUVmean	0.583	0.589	0.574	0.569	0.562	0.580	0.252
SUVsd	0.563	0.577	0.572	0.570	0.565	0.573	0.718

[a] p values of AUC between groups were compared with multi-comparison Delong's test.
[b] Volume-related parameters only, all other parameters are volume- and avidity-related parameters.

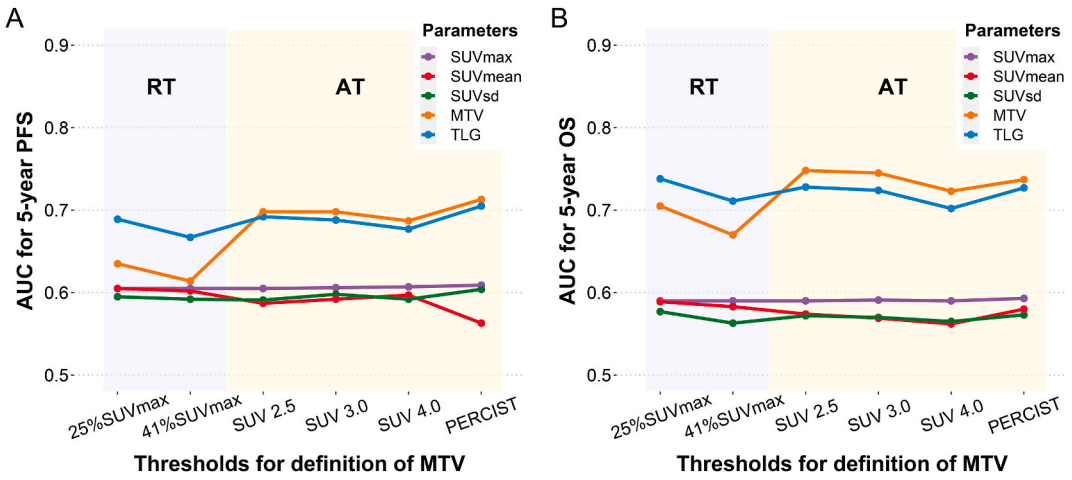

Fig. 3. AUC of metabolic parameters with different thresholds for 5-year PFS (A) and OS (B).

3.6. Optimal metabolic parameters varied with RTs and ATs

Finally, we optimized the metabolic parameters of RTs and ATs using the LASSO regression. As shown in Table 3 and Figs. S6A–B, the optimal parameters to predict survival varied with the type of threshold. When using ATs, AT-MTV (MTV-2.5, MTV-3.0, MTV-4.0, and MTV-PERCIST) was the optimal prognostic parameter for PFS and OS. However, with RTs, RT-TLG (TLG-41 % and TLG-25 %) was the optimal predictor for PFS, and combined RT-MTV and SUVmax (MTV-41 % and SUVmax, as well as MTV-25 % and SUVmax) was the optimal predictor for OS. The optimal metabolic parameters had similar C-indices predicting PFS (0.673–0.694) and OS (0.698–0.744) (Table 3). These findings indicated that composite avidity and volume parameters had better prognostic capacity in patients with ENKTCL (Fig. 6).

4. Discussion

Our study demonstrated that in patients with ENKTCL, baseline parameters including both volume and avidity (AT-MTV and TLG) have superior prognostic capacity than parameters reflecting avidity alone (SUVmax, SUVmean, and SUVsd). The thresholds used to define MTV influenced the selection and use of optimal parameters. When using ATs, AT-MTV was the optimal prognostic parameter for both PFS and OS. However, with RTs, RT-TLG was the optimal predictor for PFS, and the combination of RT-MTV and SUVmax was an optimal predictor for OS. Thus, we identified composite parameters that encompassed both avidity and volume, such as AT-MTV, RT-TLG, or combined RT-MTV and SUVmax, to predict the prognosis in patients with ENKTCL.

To our knowledge, this is the first study to quantitatively classify metabolic parameters by EFA and correlation analysis. Our results suggest that metabolic parameters can be classified into avidity-related parameters (SUVmax, SUVmean, and SUVsd), volume-related parameters (RT-MTV), and both avidity- and volume-related parameters (AT-MTV and TLG). MTV and TLG, which include volume information, demonstrated superior prognostic potential compared to avidity-related parameters in ENKTCL. Similar with our results, MTV and TLG had a higher prognostic value than SUVmax in meta-analyses of the prognostic performance of metabolic parameters in other tumors [12,13].

MTV can further identify the highly malignant component and exhibits strong correlation with patient prognosis compared to CTV. However, the definition of high metabolic area remains controversial [14]. This is the first study to compare the prognostic influence of different definitions of MTV from the perspective of the threshold types (RT vs. AT). Previous studies aimed to optimize the thresholds to define MTV and only focused on assessing the agreement or the prognostic capacity of MTV (such as MTV-2.5 vs. MTV-41 % or MTV-4.0), without combining it with other important parameters such as SUVmax and TLG [20,21]. However, our findings suggest that RTs and ATs are two distinct approaches to define MTV in ENKTCL. RTs are defined as the relative ratio of SUVmax of each tumor. RT-MTV, defined as a high metabolic region selected from the CTV using the RT value, is less susceptible to variations in the magnitude of SUVmax. On the other hand, ATs are defined by a consistent absolute SUV value for all patients, and AT-MTV, defined as a high metabolic region selected from the CTV using the fixed AT value, exhibited a strong correlation with the SUVmax of each tumor. These findings have great significance for standardizing the definition of MTV and the selection of corresponding optimal parameters in ENKTCL.

Our study suggested that avidity- and volume-related parameters, such as AT-MTV, RT-TLG, or the combination of RT-MTV and SUVmax, are preferred predictors of prognosis in ENKTCL. Notably, some previous studies on other tumors reached similar conclusions. For example, MTV was shown to be superior to TLG when using ATs [16,17], while TLG was superior to MTV when using RTs [18,19]. Moreover, when comparing MTVs with different types of thresholds, AT-MTV demonstrated a greater prognostic capacity than RT-MTV [20,27]. Further studies using different tumor types and larger sample sizes are needed to validate our findings and confirm their generalizability.

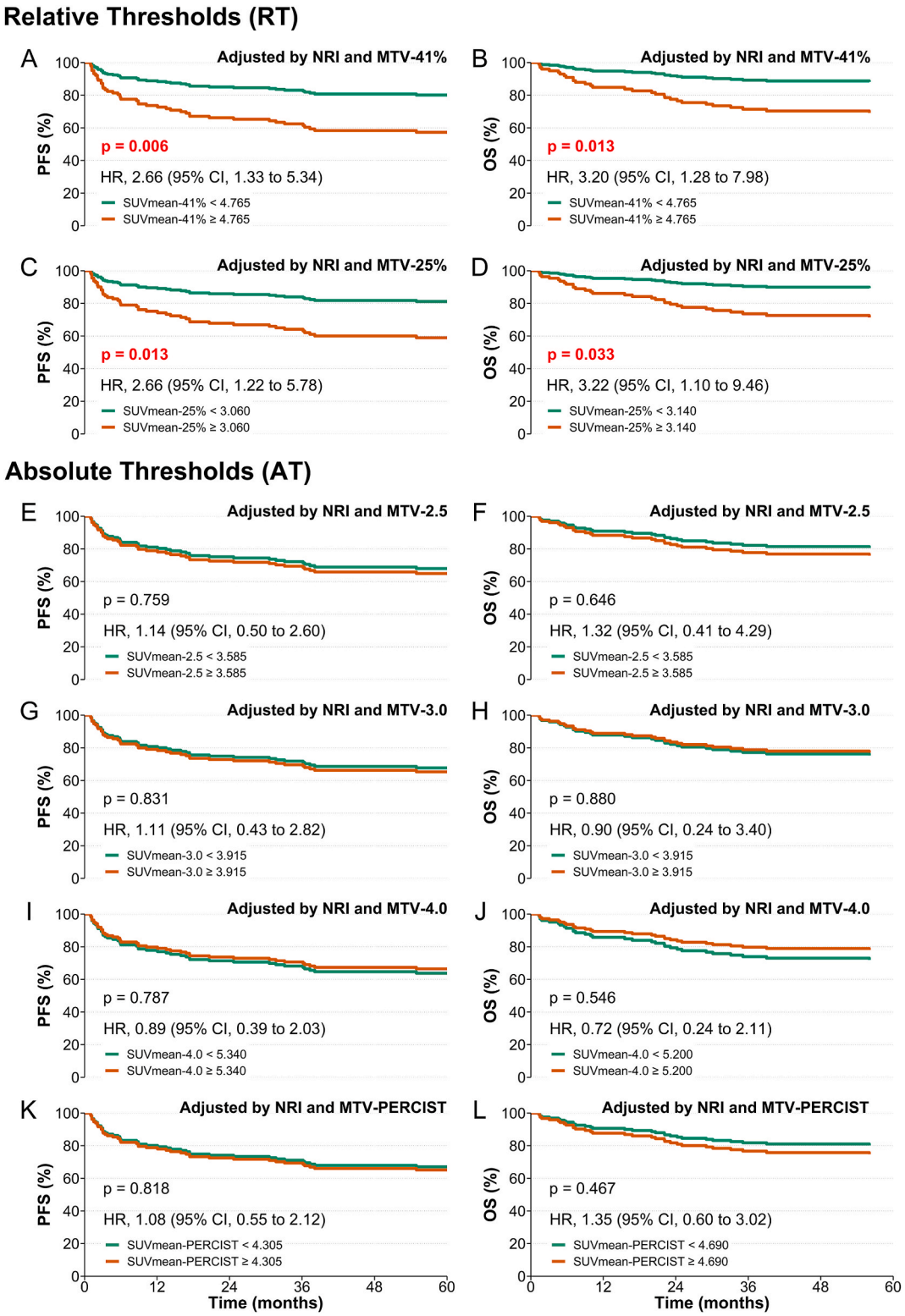

Fig. 4. Comparison of PFS (A/C/E/G/I/K) and OS (B/D/F/H/J/L) prediction of SUVmean adjusted by MTV and NRI between RTs (A/B/C/D) and ATs (E/F/G/H/I/J/K/L).

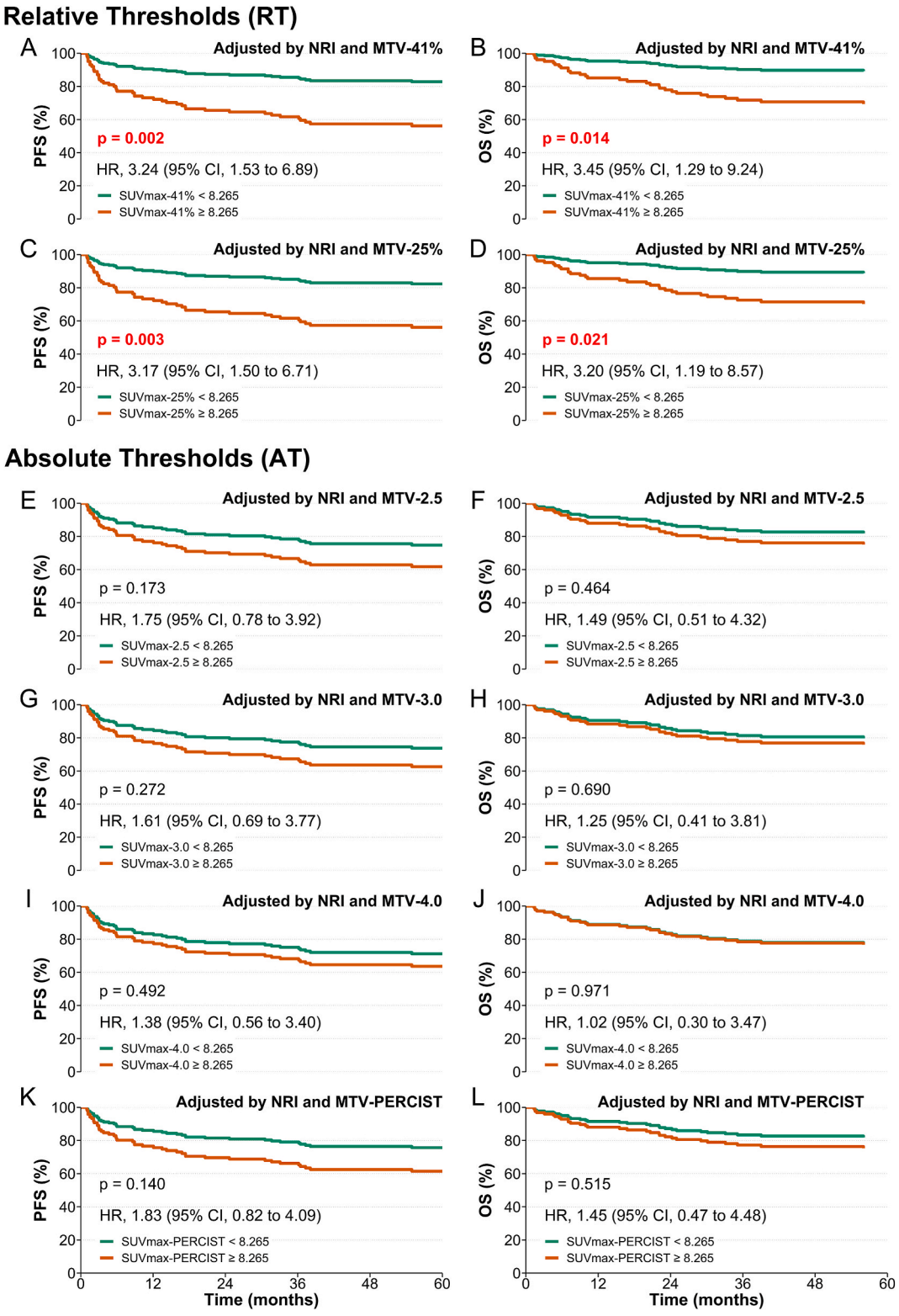

Fig. 5. Comparison of PFS (A/C/E/G/I/K) and OS (B/D/F/H/J/L) prediction of SUVmax adjusted by MTV and NRI between RTs (A/B/C/D) and ATs (E/F/G/H/I/J/K/L).

Table 3
Optimal parameters selected by LASSO within each threshold and C-index of model established by selected parameters.

Threshold	PFS		OS	
	Optimal parameters within each threshold	C-index	Optimal parameters within each threshold	C-index
RT				
41 % SUVmax	TLG-41 %	0.673	Combined MTV-41 % and SUVmax	0.726
25 % SUVmax	TLG-25 %	0.675	Combined MTV-25 % and SUVmax	0.744
AT				
SUV 2.5	MTV-2.5	0.694	MTV-2.5	0.737
SUV 3.0	MTV-3.0	0.687	MTV-3.0	0.728
SUV 4.0	MTV-4.0	0.697	MTV-4.0	0.698
PERCIST	MTV-PERCIST	0.691	MTV-PERCIST	0.729

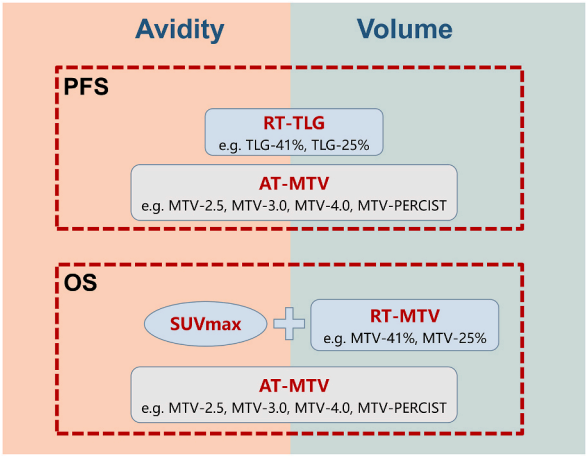

Fig. 6. Summary of the optimal metabolic parameters using RTs or ATs to predict PFS and OS in patients with ENKTCL.

Our study had several strengths. First, using quantitative analyses, we integrated metabolic parameters with different thresholds into two independent dimensions, avidity and volume. This novel approach could simplify and clarify the fundamental characteristics of metabolic parameters, thereby facilitating their optimization in future studies. Second, we conducted a comprehensive comparison of the survival differences between the definitions of MTV based on RTs and ATs. This comparison allowed a more theoretical and interpretable selection of optimal thresholds and parameters. Moreover, patients with ENKTCL included in our study were followed up for a long time. We had demonstrated the 5-year OS rate was a valid surrogate for the cure fraction in ENKTCL patients [6]. With a median follow-up time of more than 5 years in this study, PFS and OS data were relatively reliable and accurate.

This retrospective study has several limitations. Firstly, our study mainly focused on patients with early-stage ENKTCL in a registry database from a single institution, which could limit the generalizability of our findings in a different population. Further research is warranted to investigate the avidity of overall tumor burden in advanced-stage disease to predict the prognosis of these patients. In addition, more work is required to externally validate the finding using independent data from other large database. Secondly, although multivariate analysis was used to adjust for the NRI risk groups, other underlying confounders may still influence the results. Additionally, our study only adopted the most common and conventional methods for defining MTV, and did not incorporate the emerging algorithm-based adaptive threshold methods. Further studies are warranted to better understand their characteristics and delineation.

In conclusion, this comprehensive analysis and the integration of the most commonly used metabolic parameters suggests the superiority of the combinations of avidity-with volume-related parameters over avidity-related parameters in ENKTCL. Composite parameters, such as AT-MTV, RT-TLG or the combination of RT-MTV and SUVmax, showed optimal prognostic capacity in ENKTCL.

Prior presentation

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Ethical approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (No. 22/332-3534).

Informed consent

Patient consent was waived by our Institutional Review Board due to the retrospective nature of this study.

Disclaimers

The authors have no competing interests.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ying-Ming Zhu: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Pan Peng:** Methodology, Investigation, Formal analysis, Data curation. **Xin Liu:** Methodology, Data curation. **Shu-Nan Qi:** Project administration, Formal analysis, Data curation. **Shu-Lian Wang:** Data curation. **Hui Fang:** Methodology. **Yong-Wen Song:** Methodology. **Yue-Ping Liu:** Methodology. **Jing Jin:** Data curation. **Ning Li:** Data curation. **Ning-Ning Lu:** Data curation. **Hao Jing:** Methodology. **Yuan Tang:** Methodology. **Bo Chen:** Methodology. **Wen-Wen Zhang:** Methodology. **Yi-Rui Zhai:** Methodology. **Yong Yang:** Methodology. **Bin Liang:** Methodology. **Rong Zheng:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Ye-Xiong Li:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25184.

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