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Baseline Tumor Burden Assessed With AI-Guided PET/CT Total Metabolic Tumor Volume (TMTV) and LDH Levels Predict Efficacy of CAR-T in Aggressive B-Cell Lymphoma

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ABSTRACT

Disease burden is a critical determinant of outcomes in CAR-T therapy for B-cell lymphomas, and one of the most widely used techniques for its assessment is Total Metabolic Tumor Volume (TMTV) measured via [^{18}F]FDG PET/CT. Biological parameters may further refine the risk profile. We analyzed baseline [^{18}F]FDG PET/CT scans from 40 patients treated with CAR-T, using an AI-based automated segmentation algorithm to determine TMTV. Our analysis identified that a baseline TMTV greater than 48.4 cm^3 and elevated LDH independently predicted progression-free survival (PFS) after CAR-T therapy (HR 4.28, $p = 0.007$, and HR 8.20, $p < 0.001$, respectively). We then proposed a 0-to-2 risk score, assigning one point each for elevated TMTV and elevated LDH. All patients with a score of two experienced a PFS of less than 90 days following CAR-T infusion. Among the remaining patients, those with 0 points versus 1 point demonstrated a 3-month PFS of 100% versus 85%, a 6-month PFS of 92% versus 53%, and a 12-month PFS of 83% versus 53%, respectively. Importantly, patients with high baseline TMTV who achieved a TMTV reduction to less than 1.99 cm^3 by day 30 had a PFS of 66%, significantly better compared to those who did not achieve this reduction. AI-guided TMTV assessment, combined with LDH levels, provides a rapid and sensitive method for risk stratification at the bedside, which could help optimize patient management prior to CAR-T therapy.

1 | Introduction

The introduction of chimeric antigen receptor *T* cells (CAR-T) targeting CD19 has revolutionized the treatment landscape of relapsed/refractory B-cell lymphomas, achieving a cure rate of approximately 40%. However, there remains a clinical need for predictors of prognosis to identify patients who are most likely to benefit from this treatment. This would enable a better selection of patients and help avoid ineffective treatments in those with a low likelihood of achieving a response.

The factors influencing outcome following CAR-T therapy can be broadly categorized into host-related, disease-related and product-related parameters. Although age alone may not significantly affect CAR-T therapy outcomes, patients with significant comorbidities and reduced Eastern Cooperative

Lucia Leccisotti and Stefan Hohaus contributed equally to this study.

Oncology Group (ECOG) performance status scores are often deemed unsuitable candidates for this treatment. Biological characteristics of the disease and the immune microenvironment, such as lymphoma histotype [1], TP53 mutational status [2], and the composition and fitness of lymphocyte subsets along with the presence of myeloid cells with immunosuppressive function both in the microenvironment and in the blood, have been associated with outcomes following CAR-T therapy. Additionally, these factors may influence the composition of the apheresis material and the final CAR-T product [3–5].

Disease burden is a critical determinant of outcomes in CAR-T therapy [6, 7]. Parameters such as disease stage, involvement of extranodal sites and lactate dehydrogenase (LDH) levels, which reflect disease burden, are well-established prognostic factors in aggressive B-cell lymphomas and are integral components of the International Prognostic Index (IPI). Evaluation of disease burden using the [18F]fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET) combined with computer-assisted tomography (CT) scanning enables quantitative determination of the total metabolic tumor volume (TMTV). An alternative metric, whole-body total lesion glycolysis (WB-TLG) also assesses disease burden using [^{18}F]FDG PET/CT: WB-TLG integrates the glycolytic metabolic activity of tumor cells with the volume of the lesions and is calculated as the sum of the TLG (mean SUV × MTV) values of all lesions in each patient. Recent advances in software have made it possible to calculate TMTV and TLG reliably and reproducibly in a very short timeframe, suggesting that these parameters could be integrated in the standard evaluation of [^{18}F]FDG PET/CT scans in aggressive lymphomas provided they demonstrate clinical relevance.

2 | Aim

This study aims to evaluate the predictive value of metabolic tumor burden measured at baseline [^{18}F]FDG PET/CT pre CART infusion using a readily available software.

We also analyzed the impact of total metabolic tumor volume (TMTV) assessed at the evaluation 1 month after CAR-T infusion with the goal of validating its role, as this time point is not yet recognized as a standard response milestone.

3 | Patients and Methods

All adult patients with large B-cell lymphoma who received CAR-T therapy at Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome between September 2019 and November 2023 were retrospectively screened for the study.

Inclusion criterion was the availability of [^{18}F]FDG PET/CT scan images performed in the time period between lymphocyte apheresis and start of lymphodepleting chemotherapy per CAR-T infusion. For the included patients, we analyzed demographic and disease-related variables, as well as hematological and biochemical parameters collected before and during CAR-T treatment. Disease assessment with [^{18}F]FDG PET/CT was also planned at 1, 3, and 6 months after infusion.

Whole-body PET/CT was acquired using a Siemens Healthineers 3D scanner according to the procedure guidelines for tumor imaging of the European Association of Nuclear Medicine [8]. After normalization and correction for dead time, randoms and scatters, PET data were reconstructed using an iterative algorithm with the combined effect of point spread function modeling and time of flight. PET/CT images were transferred to a commercially available multimodality reading solution with molecular imaging applications for oncology. For the purpose of this study, [^{18}F]FDG PET/CT images were analyzed as follows: TMTV and whole-body total lesion glycolysis (WB-TLG) were calculated using a CE-approved AI-based automated segmentation algorithm (Lesion Scout with Auto ID, Siemens Healthineers; PERCIST-recommended liver-based threshold for lesion identification with 41% SUVmax and 4.0 SUVmax thresholds for lesion segmentation). Two independent observers verified the automatic classification of FDG-avid lesions making adjustments for erroneous regions such as sites of FDG excretion and physiologic uptake before calculating TMTVs. The automatic classification presented by Auto ID was therefore validated or not by two expert nuclear physicians before TMTV was calculated.

Response to therapy was assessed by combining [^{18}F]FDG PET/CT and clinical characteristics of patients at 1, 3 and 6 months after treatment, and subsequently at clinical signs or radiological suspicion progression. Patients with complete or partial responses (CR and PR) were considered as responders, while patients with stable disease (SD), need for retreatment, or progression (PD) were considered as failures. Progression-free survival (PFS) was calculated from the time of CAR-T infusion to the first assessment of treatment failure.

3.1 | Statistical Analysis

Categorical and continuous variables were analyzed using classical descriptive statistics, specifically Fisher's exact test or *t*-test. Inferential statistics were conducted as follows: Correlations between categorical/continuous variables and binary outcomes or survivals were assessed with logistic regression or the Cox regression model, respectively. When a cut-off value was needed, we employed the Receiver Operating Characteristic (ROC) analysis providing the optimal cut-off value with the Youden index, together with sensitivity, specificity, and Area Under the Curve (AUC). Survival outcomes were represented with the Kaplan Meier curves.

Statistical analysis was performed using NCSS 2020 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

All participants provided informed consent for the anonymized use of their data. The study was conducted in accordance with the Helsinki criteria and was approved by the local ethics committee (ID 4879 Prot 0020777/22 Amendment 02/2024).

4 | Results

Sixty-six patients were screened for the inclusion, with 37 patients meeting the eligibility criteria for the study. The median age was 56 years and 49% of the patients were male. Detailed patients' characteristics are provided in Table 1.

The median time between the baseline [^{18}F]FDG PET/CT assessment and lymphodepletion was 17 days (range 2–112 days). The median baseline TMTV and TLG were 35, 4 cm^3 (range 0–1306) and 222.4 SUV-bw × cm^3 (range 0–12318.5), respectively.

The median follow-up period was 9 months (range 1.5–41.5). Overall, 18 (49%) patients experienced failure due to refractory or progressive disease after CAR-T cells, while 19 (51%) remained in response (Deauville score 3 or less). The median PFS was 6 months, with 69%, 53%, and 49% of patients remaining alive without failure at 3, 6, and 12 months post-CAR-T, respectively.

Baseline TMTV was significantly associated with PFS in the Cox regression analysis, with B regression coefficient of 15.77 ($p < 0.001$).

A ROC analysis was performed to identify an optimal TMTV cutoff value for predicting PFS, resulting in a value of 48.4 cm^3 with 67% sensitivity and 79% specificity (AUC 70%, standard error 0.09 $p = 0.014$, 95% C.I. 48%–84%). The statistical outputs for TMTV and TLG were nearly identical, leading us to focus the analysis of TMTV alone.

Using the identified cut-off value, we compared the PFS of patients with baseline TMTV lower than 48.4 cm^3 (21 patients, 57%) to those with higher TMTV (16 patients, 43%). Patients with lower baseline TMTV had significantly better outcomes, with median PFS not reached versus 47 days ($p < 0.001$) (Figure 1). The proportions of patients alive without active disease in the two groups were 95% versus 31% at 3 months, 74% versus 20% at 6 months, and 68% versus 20% at 12 months post-CAR-T, respectively. The great majority of our PET-CT evaluations were done after bridging therapy, with a median time between PET-CT assessment and lymphodepletion of 17 days. For the few (6) patients in which PET-CT was assessed more than 30 days before CAR-T, a CT scan immediately before CAR-T confirmed that disease did not reduce or progress significantly. Also when further restricting the analysis to the 31 patients with PET-CT performed immediately before CAR-T, the results were confirmed and the cutoff of 48.4 dichotomized PFS ($p < 0.001$).

Other demographic and disease-related parameters were tested for their predictive value for PFS using Cox regression analyses. Specifically, we examined age at the time of CAR-T therapy, gender, ECOG performance status, disease stage, LDH levels, number of extranodal sites, international prognostic index (IPI), and type of CAR-T product. Notably, only LDH and baseline TMTV were found to be significant predictors of PFS, as confirmed by both univariate and multivariate analysis. Patients with elevated LDH and TMTV had hazard ratios of 5.79 and 11.56, respectively (Table 2).

TABLE 1 | Characteristics of the patient population summary of main characteristics of the study population assessed at the time of CAR-T treatment.

		All (%)	TMTV < 48.4 cm^3 (%) N = 21	TMTV > 48.4 cm^3 (%) N = 16	p
Age	Median (range)	56 (28–75)	54	57	0.923
Gender	Male (%)	18 (48)	8 (45)	10 (55)	0.141
	Female (%)	19 (52)	13 (69)	6 (31)	
Previous lines	Median (range)	2 (2–6)	2	2	0.042
Histology	DLBCL (%)	31 (77)	15 (48)	16 (52)	0.019
	PMBL (%)	6 (15)	6 (100)		
IPI	Median	2 (1–5)	2	2	0.457
LDH	Normal (%)	17 (46)	12 (71)	5 (29)	
	Above ULN (%)	20 (54)	9 (45)	11 (55)	0.117
Ferritin		291	217	356	0.886
Stage	I – II (%)	13 (35)	9 (69)	4 (31)	
	III – IV (%)	24 (65)	12 (50)	12 (50)	0.259
CAR-T product	Axi-cel (%)	21 (52)	13 (62)	8 (38)	
	Tisa-cel (%)	16 (40)	8 (50)	8 (50)	0.469
Bridging therapy	None	2 (5)	0 (0)	2 (100)	
	Radiotherapy	14 (38)	7 (50)	7 (50)	
	Systemic therapy	21 (57)	14 (67)	7 (33)	0.155

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; PMBL, primary mediastinal B-cell lymphoma; ULN, upper limit of normal; Axi-cel, axicabtagene ciloleucel; Brexu-cel, brexucabtagene autoleucel; Tisa-cel, tisagenlecleucel.

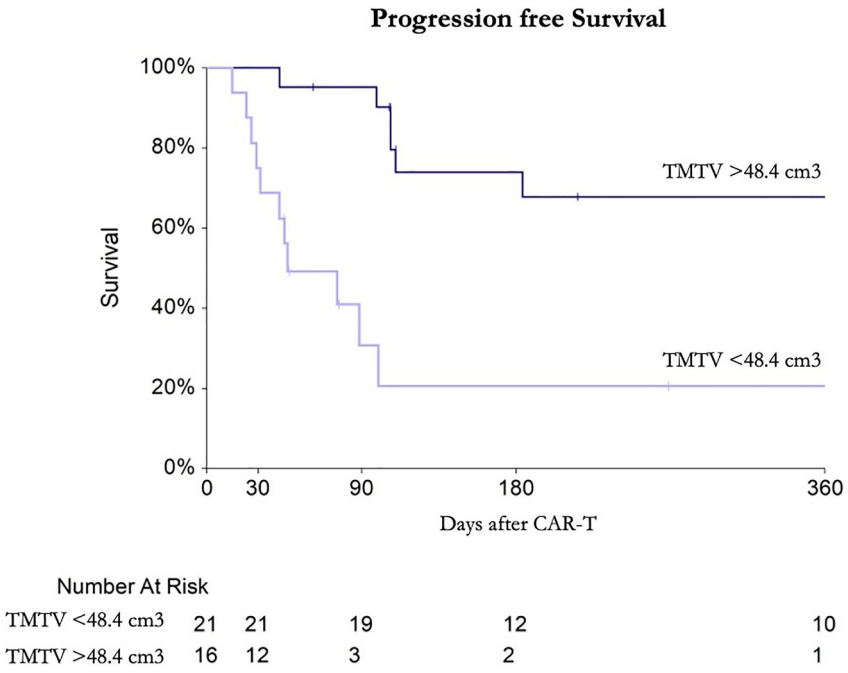


FIGURE 1 | Progression-free survival according to baseline total metabolic tumor volume (TMTV) with a cut-off of 48 cm^3.

TABLE 2 | Associations between patients-and disease-related factors and PFS in univariate and multivariate analysis. Predictive variables in univariate regression were then tested in multivariate analysis.

	Univariate			Multivariate		
	Hazard ratio	**95% CI**	***p* value**	**Hazard ratio**	**95% CI**	***p* value**
Age median	1.01	0.97–1.04	0.553			
Age cut 60	0.71	0.25–2.01	0.528			
Gender	1.27	0.49–3.26	0.616			
ECOG 0 versus 1	1.25	0.47–3.34	0.653			
Stage I–II versus III–IV	1.94	0.69–5.48	0.208			
LDH elevated	3.71	1.29–10.58	**0.014**	5.79	1.65–20.34	0.006
Ferritin	0.99	0.99–1.01	0.187			
Extranodal > 1	0.55	0.20–1.51	0.248			
IPI	1.16	0.81–1.67	0.422			
Axi-cel versus Tisa-cel	1.65	0.65–4.18	0.285			
TMTV baseline cut 48.4 cm^3	7.17	2.55–20.16	**< 0.001**	11.56	3.22–41.46	< 0.001

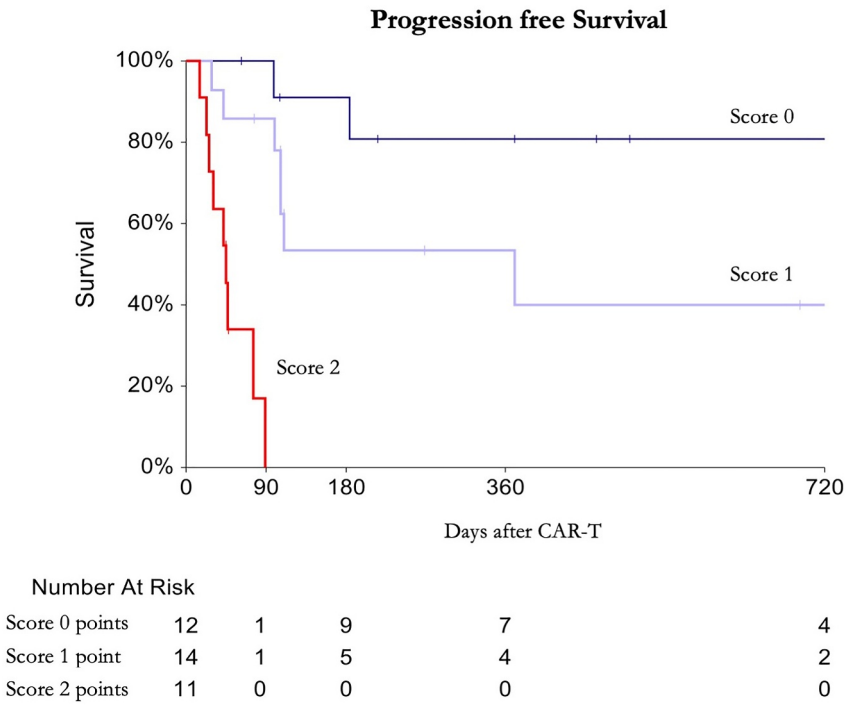
Note: Bold values denote statistical significance at the $p < 0.05$ level.
Abbreviations: IPI, international prognostic index; TMTV, total metabolic tumor volume.

We then combined LDH and TMTV to create a 0-to-2 scoring system, with one point assigned for each elevated parameter). Patients were distributed as follows: 12 patients with 0 points, 14 patients with one point, and 11 patients with two points. Despite the small sample sizes, this scoring system effectively stratified patients and predicted early failures. All patients with two points experienced a PFS of less than 90 days following CAR-T infusion. For the remaining patients, those with 0 points versus 1 point had a 3-month PFS of 100% versus 85%, a 6-month PFS of 91% versus 53%, and a 12-month PFS of 81% versus 53%, respectively (Figure 2).

We also analyzed the impact of TMTV on the post CAR-T infusion period. Cytokine Release Syndrome graded 2 or more occurred in 76% of patients, with no significant difference observed between those with low and high baseline TMTV (71% vs. 81%, $p = 0.518$). Twelve (32%) patients experienced ICANS, with no difference between low or high TMTV (29% vs. 37%, $p = 0.565$).

The expansion of CD3 + CAR + cells in peripheral blood, measured at day 7 and at day 14 following CAR-T infusion showed no significant differences between patients with low and high baseline TMTV (median 25.5 vs. 34.4 cells/microL and 16.3 vs. 22.1 cells/microL, ($p = 0.279$ and 0.285, respectively).

Notably, pre CAR-T TMTV was not associated with TMTV at early response evaluation at 1 month (M1) post CAR-T infusion



Number At Risk

Score 0 points	12	1	9	7	4
Score 1 point	14	1	5	4	2
Score 2 points	11	0	0	0	0

FIGURE 2 | Progression-free survival according to the TMTV/LDH risk score. Patients were assigned one point for having baseline TMTV > 48 cm^3 or with LDH over the normal upper limit. Stratification for having 0, one or two points was highly predictive for progression free survival or early failure.

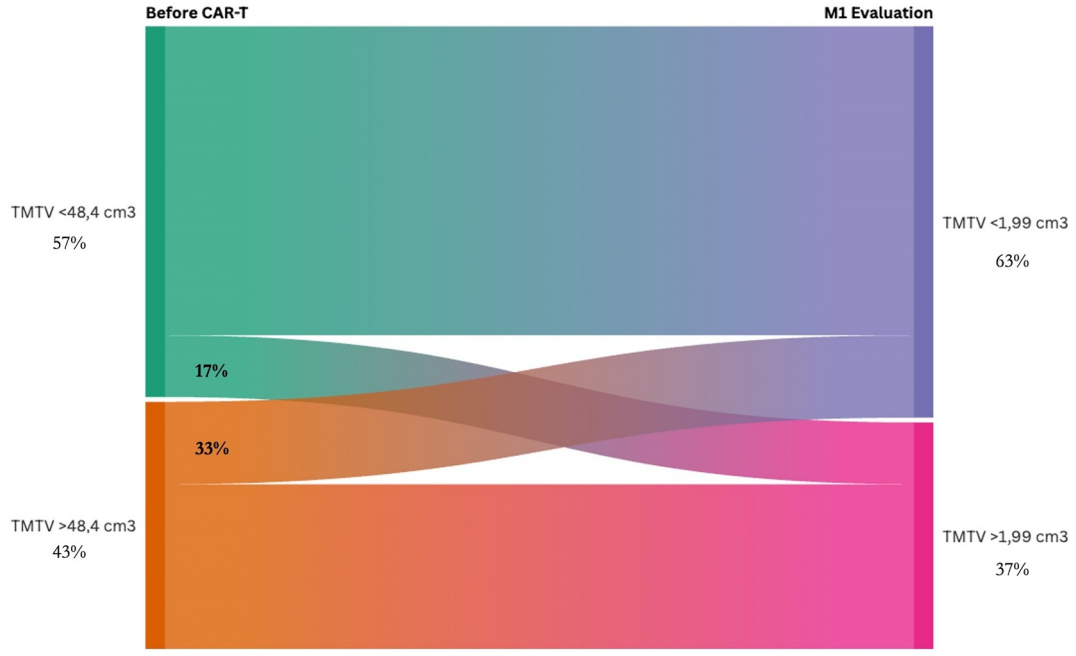


FIGURE 3 | Sankey diagram representing patients in terms TMTV before and 1 month (M1) after CAR-T therapy. For each timepoint, patients are dichotomized in two groups according to cut-off TMTV described in the text (48.4 and 1.99 cm^3 for baseline and M1 evaluation, respectively). The majority of patients with low baseline TMTV will achieve low M1 TMTV and vice versa, with some exceptions for each group: Notably, 33% patients with high baseline TMTV will be rescued by CAR-T achieving low M1 TMTV.

($p = 0.122$). We also analyzed the prognostic impact of [^{18}F]FDG PET/CT at M1. In Cox regression analysis, TMTV measured at M1 was strongly predictive of PFS ($p < 0.001$). With a cut-off value of 1.99 cm^3 reaching 60% of sensitivity and 80% of specificity (ROC AUC 72% $p = 0.008$).

Among 16 patients with a baseline TMTV > 48.4 cm^3, only four achieved a TMTV lower than 1.99 cm^3 at M1, while four patients were not evaluable at M1. (Figure 3). Those four patients showed a better outcome with respect to the patient group with a TMTV above the 1.99 cm^3 cutoff, being all in response at M3

and experiencing 6 M PFS of 66%, compared to the patients with a TMTV higher than the cutoff, who all relapsed or died before M3, $p = 0.006$). Notably, only one patient with both high baseline TMTV and elevated LDH (score 2), patient obtained M1 TMTV < 1.99 cm^3.

5 | Discussion

Our study contributes to the growing body of knowledge regarding the impact of disease burden, as measured by TMTV in [^{18}F]FDG PET/CT, on outcomes following CAR-T therapy. We defined a TMTV greater than 48.4 cm^3 during CAR-T manufacturing as a predictor of poor prognosis, with only a 20% probability of PFS at 6 months. These findings align with previous studies that have demonstrated a strong association between high tumor burden and inferior outcomes after CAR-T therapy, while excellent responses have been observed in patients achieving CR after bridging therapy.

Studies investigating the impact of TMTV on post-CAR-T outcomes vary in their methodologies for calculating TMTV and in their cutoffs for distinguishing between low and high TMTV, leading to a wide range of cutoffs [9]. Previous research has used methods such as AUC analysis of ROC curves or the median of the TMTV distribution to determine these cutoffs. The studies of Keijzer et al., Dean et al., Vercellino et al, Ababneh et al, Galtier et al., Sjöholm et al, Marchal et al, Hong et al. and Iacoboni et al. reported optimal cutoffs of 480 cm^3 [10], 147 cm^3 [11], 84 cm^3 [12], 80 cm^3 [6, 13], 39.5 cm^3 [14], 36 cm^3 [15], 26 cm^3 [16] and 25 cm^3 [17].

Our cutoff of 48.4cc falls on the lower end of reported cutoffs, likely due to the more stringent criteria we employed for TMTV calculation. We combined the 41% SUVmax threshold recommended by the EANM [8] with a 4.0 SUVmax threshold for lesion segmentation. By contrast, Keijzer et al., using a 2.5 SUVmax threshold, reported a median TMTV of 217 cm^3 before lymphodepletion, compared to 28.3 cm^3 in our study. Active tumor lesions in aggressive B-cell lymphomas typically show very high SUVmax values. Metabolic activity in tumor lesions can display significant heterogeneity due to areas of necrosis or inflammatory infiltrates, which could indicate treatment responses. While including areas of lower metabolic activity might prevent underestimation of tumor volume, focusing on the most metabolically active sites could better estimate the mass of proliferating centers of active disease.

Despite these methodological differences, TMTV consistently emerges as a robust predictor of outcomes across studies. The method we employed in our study provided a simple, automatic, rapid (under 2 min), and reliable approach with minimal manual adjustments required. However, before TMTV can be routinely applied in standard care during CAR-T therapy, there is a need for standardized calculation methods and systematic comparisons of different methodologies on large patient cohorts.

We further explored the potential of combining TMTV with other prognostic factors and identified elevated LDH levels as a significant independent predictor. In our cohort, patients with both elevated baseline LDH and TMTV had minimal chances of responding to CAR-T therapy, with a high rate of failures within the first 3 months post-infusion. Similarly, Leithner et al. recently described that combining elevated baseline TMTV with elevated LDH could predict worse PFS in CAR-T-treated patients [18]. In addition, Vercellino et al. reported that high baseline TMTV (cutoff of 80cc), elevated LDH levels, and involvement of more than one extranodal site strongly predicted PFS [6].

In conclusion, TMTV is increasingly recognized as a valuable outcome predictor in DLBCL across various therapies. Continuous-variable analysis of TMTV, as demonstrated by Locke et al., has shown that increasing tumor burden similarly impacts the efficacy of patients treated with CAR-T (axi-cel) and standard-of-care (SOC) treatments, suggesting that the negative effect of high tumor burden is not specific to any single treatment mechanism [19].

Currently, refined predictive factors are not routinely considered when assessing eligibility to CAR-T therapy. To maximize CAR-T efficacy and resources allocation, it is crucial for physicians to refine patient selection criteria. In our cohort, patients with both elevated baseline LDH and TMTV had minimal chances of responding to CAR-T therapy, highlighting the need for alternative strategies for this poor-prognosis population or further debulking strategies before CAR-T infusion.

We acknowledge several limitations of our study, including its single center, retrospective design. PET/CT was performed during CART manufacturing, and variations in timing relative to apheresis, bridging therapy and start of lymphodepletion, make it difficult to analysis dynamics of TMTV during this period. Keijzer et al. recently compared TMTV changes from apheresis to lymphodepletion, finding that median TMTV generally increased, indicating disease progression despite bridging strategies that were applied in the majority of patients [10]. Breen et al. also showed that increases in WB-TLG, a parameter strongly correlated with TMTV, from pre-apheresis to pre-lymphodepletion were associated with worse survival outcomes [20].

We further investigated the effect of TMTV dynamics by analyzing [^{18}F]FDG PET/CT results one month post-CAR-T infusion. While response evaluation using the Deauville scale did not predict PFS when considering scores 1–3 as negative and scores 4–5 as positive, stratification by high versus low TMTV using a very low cutoff of 1.99 cm^3 did predict PFS. This suggests that even patients with relatively low volumes of active disease may require further therapy due to the high risk for progression. Still, baseline TMTV should not be used as a single factor to exclude patients from CAR-T therapy, as 33% (4/12) of patients with a baseline TMTV higher than our cut-off values achieve a significant response at M1, associated with a PFS of 66% at least at short term. Conversely, significant responses at M1 in patients with high baseline TMTV and elevated LDH levels are very rare.

In conclusion, our readily available, automatic method for determining TMTV, which takes less than 2 minutes, may provide a valuable prognostic tool during CAR-T therapy. This

approach could help identify a difficult-to-treat patient cohort, even in the current era of CD19 CAR-T therapy.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request to the corresponding authors.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.70029.

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