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## Metabolic tumor volume and the survival of patients with Non-Hodgkin lymphoma treated with chimeric antigen receptor T cell therapy: a meta-analysis

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**Background:** Chimeric antigen receptor T cell (CAR-T) is a promising treatment for aggressive Non-Hodgkin lymphoma (NHL). The aim of the meta-analysis was to determine the association between metabolic tumor volumes (MTV) derived on positron emission tomography before CAR-T infusion and the survival of patients with NHL.

**Methods:** Relevant observational studies pertaining to the purpose of the metaanalysis were obtained through a search of PubMed, Web of Science, and Embase from inception of the databases to April 1, 2024. The data was combined using a random-effects model that accounted for the potential influence of betweenstudy heterogeneity.

**Results:** Fifteen observational studies were included. Pooled results showed that compared to those with a lower MTV, the NHL patients with a higher MTV before CAR-T infusion were associated with a poor progression-free survival (hazard ratio [HR]: 1.73, 95% confidence interval [CI]: 1.48 to 2.02, p < 0.001;  $I^2 = 20\%$ ) and overall survival (HR: 2.11, 95% CI: 1.54 to 2.89, p < 0.001;  $I^2 = 58\%$ ). Subgroup analysis showed that the association between MTV and survival of NHL patients after CAR-T was not significantly impacted by study design, methods for determination of MTV cutoff, or analytic models (univariate or multivariate, p for each subgroup all < 0.05). Subgroup analysis suggested a stronger association between MTV and poor survival outcomes in patients with median of lines of previous treatment of 2 or 3 as compared to those of 4 (p for subgroup difference < 0.05). Further meta-regression analyses suggested that the association between MTV and survival was not significantly affected by sample size, age, proportion of men, cutoff value of MTV, follow-up duration, or study quality scores (p all > 0.05).

**Conclusion:** A high MTV at baseline is associated with a poor survival of NHL patients after CAR-T.

## **Systematic Review Registration:** https://inplasy.com/, identifier INPLASY (INPLASY202450069).

KEYWORDS

Non-Hodgkin lymphoma, chimeric antigen receptor T, metabolic tumor volume, positron emission tomography, survival

## Introduction

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of lymphoid malignancies characterized by the proliferation of abnormal lymphocytes (1, 2). It ranks among the most prevalent hematologic malignancies globally, with its incidence steadily rising over the past few decades (3, 4). NHL encompasses various subtypes, each with distinct clinical features, prognoses, and treatment responses (5). While advancements in therapy have improved outcomes for many patients, the management of aggressive NHL subtypes remains challenging. Among the emerging treatment modalities, chimeric antigen receptor T cell (CAR-T) therapy has garnered significant attention for its remarkable efficacy in treating relapsed or refractory NHL (6, 7).

CAR-T therapy involves genetically modifying patients' T cells to express chimeric antigen receptors targeting specific antigens, such as CD19, expressed on the surface of lymphoma cells (8, 9). Upon infusion back into the patient, these engineered T cells recognize and eliminate malignant cells, leading to durable remissions in a subset of patients (8, 9). Despite its unprecedented success, not all patients respond favorably to CAR-T therapy (10, 11), highlighting the need for reliable prognostic markers to identify individuals likely to benefit from treatment. In this context, metabolic tumor volume (MTV) derived from positron emission tomography (PET) imaging has emerged as a promising biomarker for predicting treatment outcomes in NHL patients undergoing CAR-T therapy (12).

PET is a non-invasive imaging modality that provides functional information about tumor metabolism (13). By measuring the metabolic activity of tumors through the uptake of radiolabeled tracers, PET imaging enables the quantification of MTV, representing the total volume of metabolically active tumor tissue (13). High MTV levels have been associated with aggressive disease biology, treatment resistance, and poor prognosis in various cancer types, including NHL (14-16). Given its ability to capture the metabolic heterogeneity of tumors, MTV derived from PET holds potential as a prognostic biomarker for identifying patients at high risk of treatment failure or disease relapse following CAR-T therapy. Therefore, this meta-analysis aims to systematically evaluate the association between MTV and survival outcomes in NHL patients treated with CAR-T therapy, providing valuable insights into risk stratification and personalized treatment approaches in this patient population.

## Materials and methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (2020) (17, 18) was followed in this study. The Cochrane Handbook (19) for systematic review and meta-analysis was referenced throughout the study. The PRISMA Checklist of the meta-analysis is shown in Supplementary Material 1. The protocol of the study has been registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, https:// inplasy.com/) with the registration number: INPLASY202450069.

### Literature search

Three electronic databases including PubMed, Web of Science, and Embase were used for literature search with a predefined combined search term including (1) "Chimeric Antigen Receptor" OR "Chimeric Antigen Receptors" OR "Chimeric T Cell Receptors" OR "Chimeric T-Cell Receptors" OR "Chimeric Antigen Receptor T Cell" OR "CAR-T" OR "Artificial T Cell Receptors" OR "Artificial T-Cell Receptors" OR "chimeric immunoreceptors" OR "Axicabtagene ciloleucel" OR "Axi-cel" OR "KTE-C19" OR "KTEC19" OR "CTL-019" OR "CTL019" OR "Yescarta" OR "Lisocabtagene" OR "maraleucel" OR "Liso-cel" OR "JCAR-017" OR "JCAR017" OR "Breyanzi" OR "Brexucabtagene" OR "autoleucel" OR "Brexu-cel" OR "KTE-X19" OR "KTEX19" OR "Tecartus" OR "Tisagenlecleucel" OR "Tisa-cel" OR "Kymriah" OR "ART-19" OR "CART19" OR "Axicabtagene" OR "ciloleucel" OR "Idecabtagene" OR "vicleucel" OR "Ciltacabtegene" OR "autoleucel"; (2) "lymphoma" OR "non-Hodgkin lymphoma"; (3) "18F-FDG PET/CT" OR "positron emission tomography" OR "positron emission tomographycomputed tomography" OR "PET-CT" OR "PET" OR "PET CT" OR "PET/CT" OR "fluorodeoxyglucose" OR "metabolic tumor volume" OR "MTV"; and (4) "survival" OR "overall survival" OR "progression-free survival" OR "OS" OR "PFS" OR "death" OR "mortality" OR "progression" OR "prognosis" OR "cohort" OR "longitudinal" OR "prospective" OR "retrospective" OR "followed" OR "follow-up". The detailed search strategy for each database is shown in Supplementary Material 2. Only studies with human subjects and published in peer-reviewed journals in English were included. A second-round check-up for the references of the relevant

articles was also conducted. The final database search was achieved on April 1, 2024.

## Inclusion and exclusion criteria

Inclusion criteria:

- Observational studies with longitudinal follow-up published as full-length articles, such as cohort studies, nested case-control studies and *post-hoc* analysis of clinical trials;
- Studies involving adult patients with NHL who have not received CAR-T before inclusion;
- (3) A PET scan (CT or MRI) was performed before CAR-T infusion, and MTV was derived from PET scan and analyzed as a categorized variable; the cutoff for defining a high versus a low MTV was consistent with the cutoffs used among the original studies;
- (4) Compared the median progression-free survival (PFS) and/ or overall survival (OS) after CAR-T treatment between NHL patients with a high versus a low MTV at baseline, and reported the hazard ratio (HR) and 95% confidence interval (CI) for the outcomes; or these data could be calculated or estimated from the original articles. For PFS, the outcome was defined as relapse, progression, all-cause deaths or the time of last follow-up, while for OS the outcome was defined as all-cause deaths or the time of last follow-up.

We excluded reviews, editorials, preclinical studies, crosssectional studies, studies that included patients of Hodgkin lymphoma, without a PET scan at baseline, studies that did not measure MTV, studies of patients that did not receive CAR-T, or studies that did not report OS or PFS. In cases where there was potential overlap in patient population across multiple studies, only the study with the largest sample size was included in this analysis.

## Data collection and quality assessment

Two separate authors (LL and FJ) conducted a thorough search of academic literature, performed data collection and analysis, and independently assessed the quality of the studies. Any discrepancies that arose were resolved by involving the third author (HF) in discussion for final decision-making. Data on study information, design, patient characteristics including factors such as sample size, age, sex, diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), medians of previous lines of therapy including transplant, lymphodepletion method, treatment information (type of CAR-T), imaging used for PET scan, timing of PET scan, methods to determine cutoff of MTV, cutoff value of MTV, median follow-up duration, survival outcomes (median PFS or OS), analytic model (univariate or multivariate), and whether the studies and the researchers were industry supported were extracted. The assessment of study quality was carried out using the Newcastle-Ottawa Scale (NOS) (20), which involved scoring based on criteria including participant selection process, comparability among groups, and validity of outcomes. This scale utilized a rating system ranging from 1 to 9 stars; higher stars indicated better study quality. The certainty of evidence was evaluated with the five Grading of Recommendations Assessment, Development, and Evaluation (GRADE) considerations of within- and across-study risk of bias (limitations in the study design and execution or methodological quality), inconsistency (or heterogeneity), indirectness of evidence, and imprecision of the effect estimates and risk of publication bias (21). A summary offindings table was made for the outcomes based on the Cochrane Handbook (19).

## Statistical methods

The association between baseline MTV and survival of patients with NHL after CAR-T therapy was presented as the HR and 95% CI compared between patients with a high versus low MTV before CAR-T infusion. Data of HRs and standard errors were calculated based on the 95% CIs or p values, followed by a logarithmical transformation to ensure stabilized variance and normalized distribution (19). The heterogeneity among studies was assessed using the Cochrane Q test and  $I^2$  statistic (22, 23), with  $I^2 > 50\%$ indicating significant statistical heterogeneity. In view of the differences of patient diagnosis, regimen of CAR-T, cutoff of MTV, and follow-up durations etc. across the included studies, significant clinical heterogeneity was deemed among these studies, and a random-effects model was used accordingly to incorporate the potential influence of heterogeneity (19). Sensitivity analysis involving exclusion of one study at a time was conducted to assess the robustness of findings (19). Subgroup analyses were performed to investigate if features such as study design, methods for determining the cutoff of MTV, analytic models, lines of previous treatment, and whether the study/researcher was industry supported could significantly affected the meta-analysis results (19). The univariate meta-regression analysis was performed to evaluate the potential influence of these variables on the outcomes, such as sample size, mean age, proportion of men, cutoff of MTV, follow-up duration, and study quality scores (19). Publication bias estimation involved constructing funnel plots initially evaluated through visual inspection for symmetricity before being analyzed using Egger's regression test (24), where p < 0.05 indicates statistical significance. These analyses were conducted utilizing RevMan Version 5.1 from Cochrane Collaboration in Oxford, UK and Stata software version 12 from Stata Corporation in College Station, TX.

## Results

## Study inclusion

The process of selecting relevant studies for inclusion in the meta-analysis is depicted in Figure 1. Initially, 1037 potentially pertinent records were identified through thorough searches of three databases. Among these, 399 were removed due to duplication. Subsequent screening based on the titles and abstracts resulted in the



exclusion of an additional 638 studies that did not align with the aim of the meta-analysis. The full texts of the remaining 43 records underwent independent review by two authors, leading to the removal of a further 28 studies for various reasons detailed in Figure 1. Ultimately, 15 observational studies remained and were considered suitable for subsequent quantitative analyses (25–39).

## Overview of the studies' characteristics

Tables 1, 2 present the summarized characteristics of the included observational studies. Overall, four prospective studies (29, 30, 32, 33), 10 retrospective studies (25-28, 31, 34, 35, 37-39), and one post-hoc analysis (36) were included in the meta-analysis. Since one (26) of the included studies involved two independent cohorts of patients with NHL, these cohorts were included in the meta-analysis separately. These studies were published between 2019 and 2024, and performed in China, the United States, France, Sweden, Germany, Italy, Spain, and the Netherlands. All of the studies included patients with NHL, mostly of patients with relapsed or refractory large B-cell lymphoma. The sample size of the included study was generally small, varying from 16 to 175. The mean ages of the patients were 43 to 67 years, and the proportions of men varying between 44.0 to 76.9%. The median of previous lines of treatment was reported in seven studies, with 2 in one study (37), 3 in three studies (26, 31, 39), and 4 in another three studies (25, 28, 29). The methods of lymphodepletion were reported in eight studies, all of which were with fludarabine and cyclophosphamide (25-27, 29-32, 36). All of the included patients received the CAR-T treatment, with axicabtagene ciloleucel, tisagenlecleucel, brexucabtagene autoleucel, or lisocabtagene maraleucel. The PET scan was performed before CAR-T infusion, and the cutoff of MTV was determine by the medians of MTV in nine studies (25-30, 32, 33, 36), and via the Receiver Operating Characteristic (ROC) analysis in six studies (31, 34, 35, 37-39). The cutoff values for determining the high versus low MTV varied between 7.1 to 450 mL. The median follow-up duration was 7.7 to 42.6 months. The endpoint of PFS was reported in 15 cohorts (26-39), and the endpoint of OS was reported in 13 cohorts (25-27, 29-31, 33-35, 37-39). The univariate regression model was used in 11 cohorts (25, 27-30, 32, 34, 35, 37-39) in analyzing the association between MTV and survival outcome, while multivariate model was used in five cohorts (26, 31, 33, 36). Ten of the included studies or their researchers were industry supported (26, 28-33, 36, 38, 39), while five of them were not (25, 27, 34, 35, 37). The NOS of the included studies were five to nine stars, suggesting overall moderate to good study quality (Table 3).

# Meta-analysis for the association between MTV and PFS after CAR-T

Pooled results of 15 cohorts from 14 studies (26–39) suggested that compared to patients with a lower MTV at baseline, the NHL

#### TABLE 1 Patient and treatment characteristics of the included studies.

| Author year                         | Country                                   | Design       | Diagnosis                            | Number<br>of<br>patients | Mean<br>age<br>(years) | Male (%) | ECOG PS         | Previous<br>lines of<br>therapy<br>(median) | Lymphodepletion<br>method | CART-T treatment  |
|-------------------------------------|---|--------------|--------------------------------------|--------------------------|------------------------|----------|-----------------|---|---------------------------|---|
| Wang<br>2019 (25)                   | China                                     | RC           | NHL                                  | 19                       | 43                     | 63.2     | NR              | 4   | Fludarabine and Cy        | Autologous anti-CD<br>19 CAR-T, trial based,<br>containing 4–<br>1BB domain                                   |
| Dean 2020<br>C1 (26)                | USA                                       | RC           | LBCL                                 | 48                       | 63                     | 65       | 0-3             | 3   | Fludarabine and Cy        | Axi-cel   |
| Dean 2020<br>C2 ( <mark>26</mark> ) | USA                                       | RC           | LBCL                                 | 48                       | 64                     | 62.5     | 0-3             | 3   | Fludarabine and Cy        | Axi-cel   |
| Zheng<br>2020 (27)                  | China                                     | RC           | R/<br>R DLBCL                        | 13                       | 48                     | 76.9     | NR              | NR  | Fludarabine and Cy        | Autologous anti-CD<br>19 CAR-T, commercial<br>product, containing<br>CD28 or 4–<br>1BB domain                 |
| Sesques<br>2021 (28)                | France                                    | RC           | Aggressive<br>B-<br>Cell<br>lymphoma | 72                       | 60                     | 61       | 0-1 (74%)       | 4   | NR                        | Autologous anti-CD<br>19 CAR-T, commercial<br>product, co-<br>stimulatory domain<br>not specified             |
| Sjöholm<br>2022 (29)                | Sweden                                    | РС           | R/R LBCL                             | 16                       | 63                     | 44       | 0-2             | 4   | Fludarabine and Cy        | Autologous anti-CD<br>19 CAR-T (third<br>generation), trial<br>based, containing<br>CD28 and 4–<br>1BB domain |
| Winkelmann<br>2022 (30)             | Germany                                   | РС           | R/R<br>DLBCL<br>and MCL              | 34                       | 67                     | 59       | NR              | NR  | Fludarabine and Cy        | Axi-cel, tisa-cel, brexu-<br>cel, or liso-cel   |
| Guidetti<br>2023 (32)               | Italy                                     | РС           | R/R LBCL                             | 47                       | 55                     | 68       | 0-1             | NR  | Fludarabine and Cy        | Axi-cel or tisa-cel   |
| Ligero<br>2023 (33)                 | Spain                                     | РС           | R/R LBCL                             | 93                       | 59                     | 68       | 0 (34%)         | NR  | NR                        | Axi-cel or tisa-cel   |
| Galtier<br>2023 (31)                | France                                    | RC           | R/R LBCL                             | 119                      | 63                     | 62       | 0-1 (83%)       | 3   | Fludarabine and Cy        | Axi-cel or tisa-cel   |
| Zhou<br>2023 (34)                   | China                                     | RC           | DLBCL                                | 61                       | 52.1                   | 60.7     | 0-<br>1 (75.4%) | NR  | NR                        | Autologous anti-CD<br>19 CAR-T, commercial<br>product, co-<br>stimulatory domain<br>not specified             |
| Locke<br>2024 ( <mark>36</mark> )   | USA,<br>France, and<br>the<br>Netherlands | Post-<br>hoc | R/R LBCL                             | 175                      | 58                     | 61       | NR              | NR  | Fludarabine and Cy        | Axi-cel   |
| Rojek<br>2024 (38)                  | USA                                       | RC           | R/R LBCL                             | 61                       | 66                     | 70       | 0-3             | NR  | NR                        | Axi-cel, tisa-cel, or<br>liso-cel   |
| Gui<br>2024 ( <mark>35</mark> )     | China                                     | RC           | R/<br>R DLBCL                        | 38                       | 55                     | 61       | 0-2             | NR  | NR                        | Autologous anti-CD<br>19 CAR-T, commercial<br>product, co-<br>stimulatory domain<br>not specified             |
| Voltin<br>2024 (39)                 | Germany<br>and Italy                      | RC           | R/R LBCL                             | 88                       | 59                     | 62.5     | 0-<br>1 (71.6%) | 3   | NR                        | Axi-cel or tisa-cel   |
| Marchal<br>2024 (37)                | France                                    | RC           | LBCL                                 | 56                       | 60.2                   | 64       | 0-3             | 2   | NR                        | Axi-cel or tisa-cel   |

CART-T, chimeric antigen receptor T cells; RC, retrospective cohort; PC, prospective cohort; NHL, Non-Hodgkin lymphoma; LBCL, large B-cell lymphoma; R/R, relapsed or refractory; DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; Axi-cel, axicabtagene ciloleucel; tisa-cel, tisagenlecleucel; brexu-cel, Brexucabtagene autoleucel; liso-cel, lisocabtagene maraleucel; ROC, receiver operating characteristic; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; Cy, cyclophosphamide.

| Author year                         | Imaging<br>for PET | Timing of<br>PET scan                              | MTV<br>cutoff<br>determination | MTV cutoff<br>value (mL)                   | Follow-up<br>duration<br>(months) | Outcomes<br>reported | Analytic model  | Industry<br>supported |
|-------------------------------------|--------------------|--|--------------------------------|--|-----------------------------------|----------------------|---|-----------------------|
| Wang<br>2019 (25)                   | СТ                 | Before CAR-T<br>cell infusion                      | Median                         | 72   | 12.5                              | OS                   | Univariate  | No                    |
| Dean 2020<br>C1 ( <mark>26</mark> ) | СТ                 | Before CAR-T cell<br>infusion (median:<br>9 days)  | Median                         | 147.5                                      | 25                                | PFS and OS           | Multivariate (Age, bridging<br>therapy, and LDH<br>before conditioning)               | Yes                   |
| Dean 2020<br>C2 ( <mark>26</mark> ) | СТ                 | Before CAR-T cell<br>infusion (median:<br>11 days) | Median                         | 147.5                                      | 12                                | PFS and OS           | Multivariate (Age, bridging<br>therapy, and LDH<br>before conditioning)               | Yes                   |
| Zheng<br>2020 (27)                  | СТ                 | 2 Weeks before<br>CAR-T<br>cell infusion           | Median                         | 64.9                                       | 7.7                               | PFS and OS           | Univariate  | No                    |
| Sesques<br>2021 (28)                | СТ                 | Before CAR-T<br>cell infusion                      | Median                         | 48.1                                       | 15                                | PFS                  | Univariate  | Yes                   |
| Sjöholm<br>2022 (29)                | MRI                | Before CAR-T<br>cell infusion                      | Median                         | 39.5                                       | 42.6                              | PFS and OS           | Univariate  | Yes                   |
| Winkelmann<br>2022 (30)             | СТ                 | Within 2 Weeks<br>before CAR-T<br>cell infusion    | Median                         | 330  | 19.7                              | PFS and OS           | Univariate  | Yes                   |
| Guidetti<br>2023 (32)               | СТ                 | Before CAR-T cell<br>infusion (median:<br>9 days)  | Median                         | 28   | 12                                | PFS                  | Univariate  | Yes                   |
| Ligero<br>2023 (33)                 | СТ                 | Before CAR-T<br>cell infusion                      | Median                         | 177  | 30                                | PFS and OS           | Multivariate (Age, ECOG PS,<br>lines of treatment, and<br>costimulatory domain 4–1BB) | Yes                   |
| Galtier<br>2023 (31)                | СТ                 | Before CAR-T<br>cell infusion                      | ROC curve<br>analysis derived  | 80   | 12.6                              | PFS and OS           | Multivariate (Age, elevated LDH,<br>extranodal sites ≥2, and type of<br>CAR-T)        | Yes                   |
| Zhou<br>2023 (34)                   | СТ                 | Before CAR-T<br>cell infusion                      | ROC curve<br>analysis derived  | 70   | 30                                | PFS and OS           | Univariate  | No                    |
| Locke<br>2024 (36)                  | СТ                 | Before CAR-T<br>cell infusion                      | Median                         | 228.7                                      | 24.9                              | PFS                  | Multivariate (Age, LDH, and second line age-adjusted IPI)                             | Yes                   |
| Rojek<br>2024 ( <mark>38</mark> )   | NR                 | Before CAR-T cell<br>infusion (median:<br>12 days) | ROC curve<br>analysis derived  | 450  | 24                                | PFS and OS           | Univariate  | Yes                   |
| Gui<br>2024 ( <b>35</b> )           | СТ                 | Before CAR-T<br>cell infusion                      | ROC curve<br>analysis derived  | 7.1  | 18.2                              | PFS and OS           | Univariate  | No                    |
| Voltin<br>2024 (39)                 | CT<br>or MRI       | Before CAR-T<br>cell infusion                      | ROC curve<br>analysis derived  | 259 for axi-<br>cel and 11<br>for tisa-cel | 17                                | PFS and OS           | Univariate  | Yes                   |
| Marchal<br>2024 (37)                | СТ                 | Before CAR-T cell<br>infusion (median:<br>15 days) | ROC curve<br>analysis derived  | 36   | 9.7                               | PFS and OS           | Univariate  | No                    |

#### TABLE 2 PET imaging and follow-up characteristics of the included studies.

CART-T, chimeric antigen receptor T cells; PET, positron emission tomography; MTV, metabolic tumor volume; CT, computed tomography; MRI, magnetic resonance imaging; NR, not reported; ROC, receiver operating characteristic; OS, overall survival; PFS, progression-free survival; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index.

patients with a higher MTV before CAR-T infusion were associated with a poor PFS (HR: 1.73, 95% CI: 1.48 to 2.02, p < 0.001;  $I^2 = 20\%$ ; Figure 2A) with a high certainty of evidence (Table 4). Results of the "leave-one-out" sensitivity analyses showed similar results (HR: 1.66 to 1.79, p all < 0.001; Table 5). In addition, sensitivity analysis limited to studies using lymphodepletion with fludarabine and

cyclophosphamide showed similar results (HR: 1.71, 95% CI: 1.37 to 2.13, p < 0.001;  $I^2 = 22\%$ ).

The subgroup analysis showed that the association between MTV and the PFS of NHL patients after CAR-T was consistent in prospective and retrospective/*post-hoc* studies (HR: 1.60 versus 1.82, p for subgroup difference = 0.45; Figure 2B), in studies with cutoff of MTV determined

#### TABLE 3 Study quality evaluation via the Newcastle-Ottawa Scale.

| Study                     | Representativeness<br>of the<br>exposed cohort | Selection of<br>the non-<br>exposed<br>cohort | Ascertainment<br>of exposure | Outcome not<br>present<br>at baseline | Control<br>for age | Control for<br>other con-<br>founding<br>factors | Assessment<br>of outcome | Enough long<br>follow-<br>up duration | Adequacy of<br>follow-up<br>of cohorts | Total |
|---------------------------|--|---|------------------------------|---------------------------------------|--------------------|--|--------------------------|---------------------------------------|--|-------|
| Wang<br>2019 (25)         | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 6     |
| Dean 2020<br>C1 (26)      | 0  | 1   | 1                            | 1                                     | 1                  | 1  | 1                        | 1                                     | 1                                      | 8     |
| Dean 2020<br>C2 (26)      | 0  | 1   | 1                            | 1                                     | 1                  | 1  | 1                        | 1                                     | 1                                      | 8     |
| Zheng<br>2020 (27)        | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 0                                     | 1                                      | 5     |
| Sesques<br>2021 (28)      | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 6     |
| Sjöholm<br>2022 (29)      | 1  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 7     |
| Winkelmann<br>2022 (30)   | 1  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 7     |
| Guidetti<br>2023 (32)     | 1  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 7     |
| Ligero<br>2023 (33)       | 1  | 1   | 1                            | 1                                     | 1                  | 1  | 1                        | 1                                     | 1                                      | 9     |
| Galtier<br>2023 (31)      | 1  | 1   | 1                            | 1                                     | 1                  | 1  | 1                        | 1                                     | 1                                      | 9     |
| Zhou<br>2023 (34)         | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 6     |
| Locke<br>2024 (36)        | 0  | 1   | 1                            | 1                                     | 1                  | 1  | 1                        | 1                                     | 1                                      | 8     |
| Rojek<br>2024 (38)        | 1  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 7     |
| Gui<br>2024 ( <b>35</b> ) | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 6     |
| Voltin<br>2024 (39)       | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 1                                     | 1                                      | 6     |
| Marchal<br>2024 (37)      | 0  | 1   | 1                            | 1                                     | 0                  | 0  | 1                        | 0                                     | 1                                      | 5     |



overall meta-analysis; and (B), forest plots for the subgroup analysis according to study design.

by the median or ROC curve analysis (HR: 1.62 versus 1.90, p for subgroup difference = 0.30; Figure 3A), and in studies with univariate and multivariate analyses (HR: 1.64 versus 1.95, p for subgroup difference = 0.29; Figure 3B). Interestingly, a stronger association between MTV and PFS was observed for patients with median of lines of previous treatment of 2 or 3 as compared to those of 4 (HR: 2.20 versus 1.39, p for subgroup difference = 0.03; Figure 4A). In addition, a stronger association between MTV and PFS was also observed in non-industry supported studies as compared to industry supported studies (HR: 3.08 versus 1.61, p for subgroup difference = 0.02; Figure 4B).

Further meta-regression analyses suggested that the association between MTV and PFS of NHL patients after CAR-T was not

significantly affected by study sample size, mean age, proportion of men, cutoff value of MTV, follow-up duration, or study quality scores (Table 6, p all > 0.05).

## Meta-analysis for the association between MTV and OS after CAR-T

Synthesized results of 11 cohorts (25, 27-30, 32, 34, 35, 37-39) suggested a potential association between a high MTV at baseline and the poor OS of patients after CAR-T therapy (HR: 2.11, 95% CI: 1.54 to 2.89, p < 0.001;  $I^2 = 58\%$ ; Figure 5A) with a moderate certainty of evidence (Table 4). The results of the "leave-one-out"

#### TABLE 4 Summary of findings.

| Prognostic va<br>chimeric anti | alue of metab<br>igen receptor | olic tumor vol<br>T cell therapy | ume for the surviva                  | l of patients with Non-Hodgkin lymphoma treated with  |
|--------------------------------|--------------------------------|----------------------------------|--------------------------------------|---|
| Patients: pati<br>MTV on PET   | ents with Non<br>at enrollment | -Hodgkin lymj<br>; Comparison:   | phoma treated with<br>a low MTV;     | chimeric antigen receptor T cell therapy; Exposure: a high  |
| Outcomes                       | Relative effect<br>(95% CI)    | Patient<br>number (studies)      | Certainty of the<br>evidence (GRADE) | Comments  |
| Progression-<br>free survival  | HR 1.73<br>(1.48 to 2.02)      | 969<br>(14 studies)              | High                                 | A high MTV on PET at enrollment is associated with a poor PFS in NHL patients after CAR-T treatment             |
| Overall survival               | HR 2.11<br>(1.54 to 2.89)      | 694<br>(12 studies)              | Moderate <sup>a</sup>                | A high MTV on PET at enrollment is likely to be associated with a poor OS in NHL patients after CAR-T treatment |

GRADE Working Group grades of evidence; High certainty: We are very confident that the true effect lies close to that of the estimated effect. Moderate certainty: We are moderately confident in the estimated effect. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially deferent. Low certainty: Our confidence in the estimated effect is likely to be substantially different from the estimated effect. Very low certainty: We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

CI, confidence interval; HR hazard ratio; CART-T, chimeric antigen receptor T cells; PET, positron emission tomography; MTV, metabolic tumor volume; OS, overall survival; PFS, progression-free survival.

<sup>a</sup>Downgraded one point as inconsistency due to substantial heterogeneity.

sensitivity analyses further confirmed the robustness of the finding (HR: 1.80 to 2.29, p all < 0.05; Table 5). Additionally, sensitivity analysis limited to studies using lymphodepletion with fludarabine and cyclophosphamide showed similar results (HR: 2.53, 95% CI: 1.39 to 4.64, p = 0.003;  $I^2 = 75\%$ ).

Although the results were both statistically significant, the subgroup analysis suggested a stronger association between MTV and poor OS in retrospective/post-hoc studies than in the prospective studies (HR: 2.60 versus 1.30, p for subgroup difference = 0.002; Figure 5B). Further subgroup analyses showed that the association between a high MTV and poor OS was not significantly affected by methods for defining the cutoff of MTV (HR: 1.86 versus 2.40, p for subgroup difference = 0.43; Figure 6A) or the analytic models (HR: 1.56 versus 3.34, p for subgroup difference = 0.05; Figure 6B). Interestingly, a stronger association between MTV and OS was observed for patients with median of lines of previous treatment of 2 or 3 as compared to those of 4 (HR: 3.15 versus 1.28, p for subgroup difference = 0.03; Figure 7A). A similar association between MTV and OS was observed in nonindustry supported and industry supported studies (HR: 2.46 versus 2.00, p for subgroup difference = 0.53; Figure 7B).

The results of the meta-regression analysis did not suggest the association between a high MTV and poor OS was significantly modified by the study sample size, mean age, proportion of men, cutoff value of MTV, follow-up duration, or study quality scores (Table 6, p all > 0.05).

## Publication bias evaluation

Funnel plots in Figures 8A, B display the meta-analyses of the relationships between MTV at baseline with PFS and OS in NHL patients after CAR-T therapy. The symmetrical nature of the funnel plots indicates a low likelihood of publication biases. Additionally, Egger's regression test results also suggest a low risk of publication bias (p = 0.13 for the outcome of PFS and 0.25 for the outcome of OS).

## Discussion

The findings of this meta-analysis confirmed the prognostic value of MTV derived from PET in patients with NHL undergoing CAR-T therapy. The pooled results from 15 observational studies demonstrate a consistent association between higher baseline MTV and poorer survival outcomes, including PFS and OS following CAR-T therapy. Interestingly, subgroup analysis suggested a stronger association between MTV and poor OS/PFS in patients with median of lines of previous treatment of 2 or 3 as compared to those with 4. In addition, subgroup analyses revealed that this association remained robust across different study designs, methods for determining MTV cutoffs, and analytical models, suggesting the reliability and generalizability of the findings. Furthermore, metaregression analyses indicated that various factors, including sample size, patient demographics, MTV cutoff values, and study quality, did not significantly influence the observed association between MTV and survival, reinforcing the validity of the results.

The association between high MTV and poor survival outcomes in NHL patients after CAR-T therapy might be attributed to several potential mechanisms. Firstly, elevated MTV reflects a higher tumor burden and metabolic activity, indicating more aggressive disease biology and increased resistance to therapy (40). Secondly, tumors with high metabolic activity may exhibit greater heterogeneity and genomic instability, leading to treatment resistance and disease relapse (41). Moreover, the tumor microenvironment characterized by metabolic dysregulation, hypoxia, and immune evasion may contribute to therapeutic resistance and tumor progression (42). In addition, a high MTV has been related to an increased risk of CAR-T related toxicity in patients with NHL, such as the risk of grade 3+ immune effector cell-associated neurotoxicity syndrome (43, 44), which may also be an important reason for the reduced OS in these patients. Understanding these underlying mechanisms can guide the development of novel therapeutic strategies targeting metabolic vulnerabilities or enhancing CAR-T cell efficacy in high-MTV tumors.

Results of subgroup analysis findings showed a stronger association between MTV and poor OS/PFS in patients with

|                      | Meta-analysis for the a | ssociation between MT | / and PFS      |                       |
|----------------------|-------------------------|-----------------------|----------------|-----------------------|
| Dataset omitted      | HR [95% CI]             | P for effect          | l <sup>2</sup> | P for Cochrane Q test |
| Dean 2020 C1 (26)    | 1.68 [1.45, 1.95]       | < 0.001               | 14%            | 0.30                  |
| Dean 2020 C2 (26)    | 1.71 [1.46, 1.99]       | < 0.001               | 20%            | 0.24                  |
| Zheng 2020 (27)      | 1.72 [1.47, 2.02]       | < 0.001               | 23%            | 0.21                  |
| Sesques 2021 (28)    | 1.78 [1.52, 2.08]       | < 0.001               | 14%            | 0.30                  |
| Sjöholm 2022 (29)    | 1.79 [1.50, 2.13]       | < 0.001               | 22%            | 0.22                  |
| Winkelmann 2022 (30) | 1.69 [1.45, 1.98]       | < 0.001               | 18%            | 0.26                  |
| Guidetti 2023 (32)   | 1.78 [1.52, 2.09]       | < 0.001               | 13%            | 0.31                  |
| Ligero 2023 (33)     | 1.71 [1.45, 2.02]       | < 0.001               | 22%            | 0.21                  |
| Galtier 2023 (31)    | 1.72 [1.46, 2.02]       | < 0.001               | 23%            | 0.21                  |
| Zhou 2023 (34)       | 1.70 [1.45, 1.99]       | < 0.001               | 19%            | 0.25                  |
| Locke 2024 (36)      | 1.77 [1.49, 2.10]       | < 0.001               | 24%            | 0.19                  |
| Rojek 2024 (38)      | 1.76 [1.48, 2.09]       | < 0.001               | 25%            | 0.18                  |
| Gui 2024 (35)        | 1.71 [1.47, 2.00]       | < 0.001               | 21%            | 0.23                  |
| Voltin 2024 (39)     | 1.76 [1.48, 2.10]       | < 0.001               | 25%            | 0.18                  |
| Marchal 2024 (37)    | 1.66 [1.44, 1.91]       | < 0.001               | 6%             | 0.38                  |
|                      | Meta-analysis for the a | ssociation between MT | / and OS       |                       |
| Dataset omitted      | HR [95% CI]             | P for effect          | l <sup>2</sup> | P for Cochrane Q test |
| Wang 2019 (25)       | 2.20 [1.57, 3.09]       | < 0.001               | 61%            | 0.003                 |
| Dean 2020 C1 (26)    | 1.98 [1.45, 2.70]       | < 0.001               | 55%            | 0.01                  |
| Dean 2020 C2 (26)    | 2.02 [1.47, 2.76]       | < 0.001               | 58%            | 0.006                 |
| Zheng 2020 (27)      | 2.05 [1.48, 2.82]       | < 0.001               | 59%            | 0.005                 |
| Sjöholm 2022 (29)    | 2.29 [1.65, 3.19]       | < 0.001               | 46%            | 0.04                  |
| Winkelmann 2022 (30) | 2.18 [1.56, 3.05]       | < 0.001               | 61%            | 0.003                 |
| Ligero 2023 (33)     | 2.23 [1.57, 3.17]       | < 0.001               | 61%            | 0.003                 |
| Galtier 2023 (31)    | 1.80 [1.38, 2.35]       | < 0.001               | 36%            | 0.10                  |
| Zhou 2023 (34)       | 2.04 [1.47, 2.83]       | < 0.001               | 59%            | 0.005                 |
| Rojek 2024 (38)      | 2.21 [1.53, 3.20]       | < 0.001               | 62%            | 0.003                 |
| Gui 2024 (35)        | 2.10 [1.53, 2.88]       | < 0.001               | 61%            | 0.003                 |
| Voltin 2024 (39)     | 2.26 [1.58, 3.23]       | < 0.001               | 61%            | 0.003                 |
| Marchal 2024 (37)    | 2.08 [1.49, 2.90]       | < 0.001               | 60%            | 0.003                 |

TABLE 5 Sensitivity analysis by excluding one dataset at a time for the association between MTV and survival outcomes.

MTV, metabolic tumor volume; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

median of lines of previous treatment of 2 or 3 as compared to those with 4, which suggests that the prognostic value of MTV on PET scans in patients with NHL undergoing CAR T-cell therapy might be modulated by the number of previous treatment lines. However, these findings suggest that patients with fewer lines of treatment may have a higher risk of poor outcome (PFS/OS), which seems paradoxical considering patients with fewer lines of treatment are expected to have fitter T-cells (45, 46) and better treatment outcomes after CAR-T therapy. It seems that there are other confounding factors accounting for these results, such as potentially increased rate of CAR-T toxicities or infections in patients with fewer lines of treatment, which were not assessed in this meta-analysis. Besides, meta-analysis for the outcomes of PFS and OS analysis showed moderate and high heterogeneity, respectively. Therefore the results should be interpreted very cautiously. Moreover, for the subgroups with the median of previous lines treatment of 4, very few studies (only 2) were available, which probably is too small to capture the true effect.

|  | y or Subgroup   | log[Hazard Ratio]  | SE  | Weight   | IV, Random, 95% CI   | IV       | . Rando                          | m, 95%                | СІ        |        |
|--|---|--|---|--|--|----------|----------------------------------|-----------------------|-----------|--------|
| 1.3.1  | Median  |  |   |  |  |          |                                  |                       |           |        |
| Dean   | 1 2020 C1   | 1.203  | 0.45678   | 2.8%   | 3.33 [1.36, 8.15]  |          |                                  |                       |           |        |
| Dean   | 1 2020 C2   | 1.0784   | 0.53078   | 2.1%   | 2.94 [1.04, 8.32]  |          |                                  |                       |           |        |
| Zheng  | ng 2020   | 0.9439   | 0.59679   | 1.7%   | 2.57 [0.80, 8.28]  |          |                                  |                       |           |        |
| Sesqu  | lues 2021   | 0.2311   | 0.19679   | 11.1%  | 1.26 [0.86, 1.85]  |          |                                  | <u> </u>              |           |        |
| Sjoho  | olm 2022  | 0.392  | 0.15846   | 14.7%  | 1.48 [1.08, 2.02]  |          |                                  | <u> </u>              |           |        |
| Winke  | elmann 2022   | 1.0886   | 0.45918   | 2.7%   | 2.97 [1.21, 7.31]  |          | _                                | -                     |           |        |
| Guide  | etti 2023   | 0.239  | 0.10010   | 9.7%   | 1.27 [0.88, 1.84]  |          |                                  |                       |           |        |
| Ligen  | 0 2023<br>o 2024  | 0.0981   | 0.23335   | 0.7%   | 2.01 [1.27, 3.16]  |          | ļ                                |                       |           |        |
| Subt   | e 2024<br>total (95% CI)  | 0.4055   | 0.22555   | 64.9%  | 1.62 [1.33, 1.98]  |          |                                  | •                     |           |        |
| Heter  | rogeneity: Tau <sup>2</sup> = 0   | .02: Chi² = 10.54. d   | f = 8 (P = (  | ).23): l <sup>2</sup> = 2  | 24%  |          |                                  |                       |           |        |
| Test f   | for overall effect: Z   | = 4.81 (P < 0.0000   | 1)  | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,  |  |          |                                  |                       |           |        |
| 1.3.2  | ROC curve analy   | sis derived  |   |  |  |          |                                  |                       |           |        |
| Galtie   | er 2023   | 0.7178   | 0.27307   | 6.8%   | 2.05 [1.20, 3.50]  |          |                                  |                       |           |        |
| Zhou   | 1 2023  | 0.9969   | 0.42568   | 3.1%   | 2.71 [1.18, 6.24]  |          |                                  |                       |           |        |
| Rojek  | k 2024  | 0.4947   | 0.20841   | 10.3%  | 1.64 [1.09, 2.47]  |          |                                  | -                     |           |        |
| Gui 2  | 2024  | 1.1053   | 0.61567   | 1.6%   | 3.02 [0.90, 10.09]   |          | +                                | •                     |           | -      |
| Voltin   | n 2024  | 0.4886   | 0.19777   | 11.1%  | 1.63 [1.11, 2.40]  |          |                                  |                       |           |        |
| March  | hal 2024  | 1.4398   | 0.49801   | 2.3%   | 4.22 [1.59, 11.20]   |          |                                  | -                     | •         | -      |
| Subto  | total (95% CI)  |  |   | 35.1%  | 1.90 [1.52, 2.39]  |          |                                  | •                     |           |        |
| Heter  | rogeneity: Tau <sup>2</sup> = 0   | .00; Chi <sup>2</sup> = 5.01, df   | = 5 (P = 0.   | 42); I <sup>2</sup> = 0 <sup>4</sup>   | %  |          |                                  |                       |           |        |
| Test f   | tor overall effect: Z   | = 5.54 (P < 0.0000   | 1)  |  |  |          |                                  |                       |           |        |
| Total  | l (95% Cl)  |  |   | 100.0%   | 1.73 [1.48, 2.02]  |          |                                  | ♦                     |           |        |
| Heter  | rogeneity: Tau <sup>2</sup> = 0   | .02; Chi² = 17.39, d   | f = 14 (P =   | 0.24); l <sup>2</sup> =  | : 20%  |          |                                  | 2                     | 5 /       | +      |
| Test f   | for overall effect: Z   | = 6.93 (P < 0.0000   | 1)  |  |  | 0.1 0.2  | 0.5 1                            | 2                     | 5         | 0      |
|  | e 1 1.00  | 01:2 4 07  | 10 4 10   |  |  |          |                                  |                       |           |        |
| Test f   | for subaroup differe  | ences: $Cni^{+} = 1.07$ .  | df = 1 (P =   | 0.30). l <sup>2</sup> =  | 6.5%   |          |                                  |                       |           |        |
| Test f   | for subaroud differe  | ences: Chi* = 1.07.  | df = 1 (P =   | 0.30).   <sup>2</sup> =  | 6.5%<br>Hazard Ratio   |          | Hazard                           | Ratio                 |           |        |
| BStudy   | for subaroup differe  | log[Hazard Ratio]  | dt = 1 (P =<br>SE   | 0.30).   <sup>2</sup> =  | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl   | IV       | Hazard<br>, Rando                | Ratio<br>m. 95%       | CI        |        |
| B<br><u>Study</u><br>1.4.1   | tor subaroub differe<br>ly or Subgroup<br>Univariate  | log[Hazard Ratio]  | at = 1 (P =<br>SE   | 0.30).   <sup>2</sup> =  | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl   |          | Hazard<br>. Rando                | Ratio<br>m. 95% (     | CI        |        |
| Test f<br>B<br><u>Study</u><br>1.4.1<br>Zheng  | tor subgroup differently or Subgroup<br>Univariate<br>1g 2020   | Iog[Hazard Ratio]<br>0.9439  | of = 1 (P =<br><u>SE</u><br>0.59679   | 0.30). I <sup>2</sup> =<br><u>Weight</u><br>1.7%   | : 6.5%<br>Hazard Ratio<br><u>_IV. Random, 95% CI</u><br>2.57 [0.80, 8.28]  |          | Hazard                           | Ratio<br>m. 95% (     | <u>CI</u> |        |
| B <u>Study</u><br>1.4.1<br>Zheng<br>Sesqu  | for subaroup differently or Subgroup<br>Univariate<br>19 2020<br>19 2021  | Inces: Chi <sup>2</sup> = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311   | 0.59679<br>0.19679  | 0.30). I <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%  | : 6.5%<br>Hazard Ratio<br><u>IV. Random, 95% Cl</u><br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]  |          | Hazard<br>. Rando<br>            | Ratio<br>m, 95%       | <u>cı</u> |        |
| B <u>Study</u><br>1.4.1<br>Zheng<br>Sesqu<br>Sjöho   | tor subaroup different<br>v or Subgroup<br>Univariate<br>Ig 2020<br>jues 2021<br>olm 2022   | ences: Chi <sup>+</sup> = 1.07.<br><u>log[Hazard Ratio]</u><br>0.9439<br>0.2311<br>0.392   | 0.59679<br>0.19679<br>0.15846   | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%   | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]  |          | Hazard<br>. Rando<br>            | Ratio<br>m. 95% (     | <u>cı</u> |        |
| Test f<br>B <u></u><br>1.4.1<br>Zheng<br>Sjöho<br>Winke  | tor subaroub different<br>v or Subgroup<br>Univariate<br>g 2020<br>jues 2021<br>olm 2022<br>selmann 2022  | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886   | 0.59679<br>0.19679<br>0.15846<br>0.45918  | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]   |          | Hazard<br>Rando                  | Ratio<br>m. 95% (     | <u>CI</u> |        |
| Test f<br>B <u></u><br>1.4.1<br>Zheng<br>Sjöho<br>Winke<br>Guide   | tor Subgroup<br>Univariate<br>g 2020<br>jues 2021<br>olm 2022<br>ielmann 2022<br>etti 2023  | Inces: CnF = 1.07.<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.18816   | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%  | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]  |          | Hazard<br><u>Arando</u>          | Ratio<br>m. 95% (     | <u>CI</u> |        |
| Test f<br>B <u>Study</u><br>1.4.1<br>Zheng<br>Sjöho<br>Winke<br>Guide<br>Zhou  | ly or Subgroup<br>Univariate<br>Ig 2020<br>Jues 2021<br>olm 2022<br>elemann 2022<br>etti 2023   | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.42568  | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%  | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]   | 11       | Hazard                           | Ratio<br>m. 95% (     | CI        |        |
| Test f<br>B <u>Study</u><br>1.4.1<br>Zheng<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek   | tor subaroub difference<br>Univariate<br>Ig 2020<br>Jues 2021<br>olm 2022<br>celmann 2022<br>etti 2023<br>k 2024  | ances: ChF = 1.07.<br>0.9439<br>0.2311<br>0.392<br>1.0866<br>0.239<br>0.9969<br>0.4947   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.42568<br>0.20841   | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%   | 6.5%<br>Hazard Ratio<br>IV. Random. 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]  | IV       | Hazard<br><u>, Rando</u><br>     | Ratio<br>m. 95%  <br> | CI        |        |
| Test f<br>B<br><u>Study</u><br>1.4.1<br>Zheng<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2  | ly or Subgroup<br>Univariate<br>ng 2020<br>jues 2021<br>olm 2022<br>telmann 2022<br>etti 2023<br>i 2023<br>k 2024<br>2024   | Inces: Chr = 1.07.<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.42568<br>0.20841<br>0.61567  | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]  |          | Hazard<br><u>Rando</u><br>       | Ratio<br>m. 95% (     | <u>CI</u> |        |
| Test f<br>B <u>Study</u><br>1.4.1<br>Zheny<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Vottin   | tor Subgroup<br>Univariate<br>ng 2020<br>jues 2021<br>olm 2022<br>kelmann 2022<br>etti 2023<br>i 2023<br>k 2024<br>2024<br>n 2024   | ances: Chr = 1.07.<br>log[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.19777   | 0.30).   <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]   | <u> </u> | Hazard<br><u>Rando</u><br>-<br>- | Ratio<br>m. 95% (     | <u>CI</u> |        |
| Test f<br>B<br>Study<br>1.4.1<br>Zheny<br>Sesq<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct   | tor subdroub difference<br>Univariate<br>Ig 2020<br>Jues 2021<br>Jues 2021<br>Jues 2022<br>selmann 2022<br>etti 2023<br>k 2024<br>2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024  | Inces: Chr = 1.07.<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9669<br>0.4947<br>1.1053<br>0.4886<br>1.4398   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.20841  | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%  | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]   | IV       | Hazardo                          | Ratio<br>m. 95% (     | CI        |        |
| B <u>Study</u><br>1.4.1<br>Zheng<br>Sjöho<br>Winke<br>Gui2<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct  | tor subgroup<br>Univariate<br>1g 2020<br>Jues 2021<br>Jues 2021<br>Jolm 2022<br>Leimann 2022<br>etti 2023<br>k 2024<br>2024<br>2024<br>2024<br>Jold 195% CI)  | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.19777   | 0.30).   <sup>2</sup> =<br><u>Weight</u><br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%   | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> </ul>  | ιv       | Hazardo                          | Ratio<br>m. 95% (     | CI        |        |
| Test f<br>B<br>Study<br>1.4.1<br>Zheny<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Vottin<br>Marct<br>Subtx<br>Heter<br>Test f  | tor Subgroup different<br>Univariate<br>ag 2020<br>jues 2021<br>olm 2022<br>etil 2023<br>i 2023<br>i 2023<br>i 2023<br>k 2024<br>in 2024<br>in 2024<br>in 2024<br>in 2024<br>in 2024<br>otal (95% CI)<br>for overall effect: Z  | Inces: Ch <sup>2</sup> = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.19777<br>0.49801<br>f = 9 (P = 0  | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); 1 <sup>2</sup> = :   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]<br>1.64 [1.36, 1.99]<br>25%   |          | Hazard<br><u>Rando</u><br>       | Ratio<br>m. 95%       | <u>cı</u> |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct<br>Subte<br>Heter<br>Test f  | ly or Subgroup<br>Univariate<br>lig 2020<br>jues 2021<br>olm 2022<br>telmann 2022<br>etti 2023<br>i 2023<br>k 2024<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co24<br>co26<br>co3<br>co27<br>co3<br>co3<br>co26<br>co3<br>co3<br>co3<br>co3<br>co24<br>co3<br>co3<br>co3<br>co3<br>co3<br>co3<br>co3<br>co3   | Inces: Ch <sup>2</sup> = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000  | SE           0.59679           0.19679           0.15846           0.45918           0.42568           0.20841           0.20841           0.20841           0.41567           0.19679           0.20841           0.42568           0.20841           0.4801           f = 9 (P = (1))     | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); 1 <sup>2</sup> = ;   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]<br>1.64 [1.36, 1.99]<br>25%   |          | Hazard                           | Ratio<br>m. 95%       | <u></u>   | -      |
| B<br>Study<br>1.4.1<br>Zheny<br>Sesq<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui2<br>Voltin<br>Marct<br>Subte<br>Heter<br>Test f  | tor subdroub differ<br>(y or Subgroup<br>Univariate<br>19 2020<br>19 2020<br>19 2022<br>10 2022<br>10 2022<br>10 2022<br>10 2023<br>12 2024<br>12 20 20<br>12 20 | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.49801<br>f = 9 (P = (<br>1)  | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); l <sup>2</sup> = ;   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]<br>1.64 [1.36, 1.99]<br>25%   |          | Hazard                           | Ratio<br>m. 95%       | <u></u>   |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sijöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>March<br>Subto<br>Heter<br>Test f  | tor Subdroub different<br>Univariate<br>1g 2020<br>1gues 2021<br>1gues 2021<br>1gues 2021<br>1gues 2022<br>1gues 2022<br>1gues 2022<br>1gues 2022<br>1gues 2022<br>1gues 2022<br>1gues 2023<br>1gues 2024<br>1gues 202  | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000  | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.49801<br>f = 9 (P = 0<br>1)<br>0.45678   | 0.30). I <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>).21); I <sup>2</sup> = :   | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95%       | cı        |        |
| B <u></u>  | tor Subgroup differ<br>Univariate<br>19 2020<br>19 2020<br>19 2022<br>10 2022<br>10 2022<br>10 2023<br>12 2023<br>12 2023<br>12 2023<br>12 2023<br>12 2024<br>12 202  | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0866<br>0.239<br>0.969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000   | SE           0.59679           0.18679           0.15846           0.45918           0.42568           0.20841           0.61567           0.49801           f = 9 (P = 0           0.456678           0.30278  | 0.30). I <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); I <sup>2</sup> = ;<br>2.8%<br>2.8%<br>2.7%   | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random, 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | CI        | -      |
| B<br>Study<br>1.4.1<br>Zheny<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct<br>Subty<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Ligerr   | tor Subgroup different<br>Univariate<br>Ig 2020<br>Jues 2021<br>Joim 2022<br>Leilmann 2022<br>etti 2023<br>1 2023<br>1 2023<br>1 2024<br>2024<br>2024<br>2024<br>2024<br>1 2024<br>1 2020<br>1      | Inces: ChP = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0866<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6881   | SE           0.59679           0.18679           0.15846           0.45918           0.45918           0.42568           0.20841           0.20841           0.61567           0.49801           f = 9 (P = 0           1)           0.45678           0.53078           0.23335            | 0.30). I <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); I <sup>2</sup> = ;<br>2.8%<br>2.1%<br>8.7%   | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random, 95% CI</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | <u></u>   | -      |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>March<br>Subta<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Ligero<br>Galtic   | tor subdroub differ<br>(y or Subgroup<br>Univariate<br>19 2020<br>19 2020<br>19 2020<br>19 2021<br>10 2022<br>10 2022<br>10 2022<br>10 2023<br>12 2023<br>12 2023<br>12 2024<br>10 2024   | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi² = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178   | SE           0.59679           0.19679           0.15846           0.42568           0.20841           0.61567           0.49801           f = 9 (P = (1))           0.45678           0.53078           0.53335           0.23335           0.27307  | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); l <sup>2</sup> = :<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>0.2%   | 6.5%<br>Hazard Ratio<br>IV. Random, 95% CI<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]<br>1.64 [1.36, 1.99]<br>25%<br>3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.00]<br>4.50 [0.27, 3.50]<br>4.50 |          | Hazard                           | Ratio m. 95% (        | <u></u>   |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesq<br>Sjöho<br>Winke<br>Gui 2<br>Voltin<br>Marct<br>Subto<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Liger<br>Galtie<br>Locke  | tor Subdroub differ<br>Univariate<br>1g 2020<br>1gues 2021<br>olm 2022<br>elemann 2022<br>etit 2023<br>1z023<br>k 2024<br>2024<br>2024<br>2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024<br>1 2024<br>1 2020<br>1 2020<br>1 2020<br>1 2020<br>1 2023<br>1 2020<br>1 2020<br>1 2024<br>1 2020<br>1 2020<br>1 2020<br>1 2024<br>1 2020<br>1 20      | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.49801<br>f = 9 (P = 0<br>1)<br>0.456678<br>0.23378<br>0.23378<br>0.2335  | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>).21); 1 <sup>2</sup> = :<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>2.96%  | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | <u></u>   |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesq<br>Sjöno<br>Winkk<br>Gui de<br>Zhou<br>Rojek<br>Gui 2<br>Volla<br>March<br>Subto<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Ligero<br>Galtie<br>Lockk<br>Subto                                | tor subdroub differ<br>Univariate<br>1g 2020<br>1g 2020<br>1g 2020<br>1g 2020<br>1g 2022<br>1g 2023<br>1g 2023<br>1g 2023<br>1g 2023<br>1g 2023<br>1g 2023<br>1g 2024<br>1g 2026<br>1g 202  | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>0.2; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055<br>.00; Chi <sup>2</sup> = 3.40, df   | 0.59679<br>0.19679<br>0.15846<br>0.45918<br>0.42568<br>0.20841<br>0.61567<br>0.49801<br>f = 9 (P = 0<br>1)<br>0.45678<br>0.53078<br>0.2335<br>0.27307<br>0.22355<br>= 4 (P = 0.   | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>0.3%<br>10.3%<br>1.6%<br>11.1%<br>0.3%<br>2.3%<br>70.4%<br>0.21); 1 <sup>2</sup> = ;<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>29.6%<br>49; 1 <sup>2</sup> = 0' | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | <u></u>   |        |
| B <u>Study</u><br>1.4.1<br>Zheng<br>Sjöno<br>Winkk<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct<br>Subto<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Ligero<br>Galtie<br>Locke<br>Subto<br>Heter                           | tor subdroub differ<br>(y or Subgroup<br>Univariate<br>19 2020<br>19 2020<br>19 2020<br>19 2020<br>19 2022<br>19 2023<br>19 2023<br>19 2023<br>19 2023<br>19 2023<br>19 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2020<br>10 2020   | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4866<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055<br>.00; Chi <sup>2</sup> = 3.40, df<br>= 5.18 (P < 0.0000   | $\begin{array}{c} SE \\ 0.59679 \\ 0.19679 \\ 0.15846 \\ 0.45918 \\ 0.18816 \\ 0.42568 \\ 0.20841 \\ 0.61567 \\ 0.19777 \\ 0.49801 \\ f = 9 (P = 0) \\ 1) \\ \hline \\ 0.45678 \\ 0.53078 \\ 0.23355 \\ 0.27307 \\ 0.22355 \\ = 4 (P = 0. \\ 1) \end{array}$                                | 0.30). 1 <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21); 1 <sup>2</sup> = ;<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>29.6%<br>49); 1 <sup>2</sup> = 0'  | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | ci        |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesqu<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>March<br>Subte<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Liger<br>Galtie<br>Locke<br>Subte<br>Heter<br>Test f             | tor subdroub differ<br>(y or Subgroup<br>Univariate<br>19 2020<br>19 2020<br>19 2020<br>19 2022<br>10 2022<br>10 2022<br>10 2022<br>10 2023<br>12 2023<br>12 2023<br>12 2024<br>10 2024   | Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055<br>.00; Chi <sup>2</sup> = 3.40, df<br>= 5.18 (P < 0.0000   | at = 1 (P =<br><u>SE</u><br>0.59679<br>0.19679<br>0.15846<br>0.42568<br>0.20841<br>0.61567<br>0.49801<br>f = 9 (P = (1)<br>0.45678<br>0.53078<br>0.23335<br>0.27307<br>0.22355<br>= 4 (P = 0.<br>1)   | 0.30).   <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21);   <sup>2</sup> = ;<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>9.3%<br>29.6%<br>49);   <sup>2</sup> = 0''<br>100.0%                       | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random, 95% CI</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> <li>3.33 [1.36, 8.15]</li> <li>2.94 [1.04, 8.32]</li> <li>2.01 [1.27, 3.18]</li> <li>2.05 [1.20, 3.50]</li> <li>1.50 [0.97, 2.32]</li> <li>1.95 [1.51, 2.51]</li> <li>%</li> </ul>  |          | Hazard                           | Ratio<br>m. 95% (     | ci<br>    |        |
| B<br>Study<br>1.4.1<br>Zheng<br>Sesq<br>Sjöho<br>Winke<br>Gui 2<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>March<br>Subto<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Ligero<br>Galtie<br>Locke<br>Subto<br>Heter<br>Test f             | tor Subdroub different<br>(y or Subgroup<br>Univariate<br>19 2020<br>19 2020<br>19 2020<br>19 2020<br>19 2022<br>19 2023<br>19 2023<br>19 2023<br>19 2023<br>19 2023<br>19 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2024<br>10 2020<br>10 2024<br>10 2020<br>10 2020<br>10 2024<br>10 2020<br>10 2020<br>10 2024<br>10 2020<br>10 2020<br>10 2024<br>10 2020<br>10 20<br>10 2020<br>10 200<br>10 2020<br>10 2020<br>10 2020   | Inces: Ch <sup>2</sup> = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>0.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055<br>.00; Chi <sup>2</sup> = 3.40, df<br>= 5.18 (P < 0.0000  | $\begin{array}{c} \text{SE} \\ 0.59679 \\ 0.19679 \\ 0.15846 \\ 0.45918 \\ 0.42568 \\ 0.20841 \\ 0.61567 \\ 0.49801 \\ f = 9 (P = 0) \\ 1) \\ 0.45678 \\ 0.2335 \\ 0.27307 \\ 0.22355 \\ = 4 (P = 0. \\ 1) \\ f = 14 (P = 0. \\ 1) \end{array}$   | 0.30).   <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21);   <sup>2</sup> = ;<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>29.6%<br>49);   <sup>2</sup> = 0'<br>100.0%<br>0.24);   <sup>2</sup> =             | <ul> <li>6.5%</li> <li>Hazard Ratio</li> <li>IV. Random. 95% Cl</li> <li>2.57 [0.80, 8.28]</li> <li>1.26 [0.86, 1.85]</li> <li>1.48 [1.08, 2.02]</li> <li>2.97 [1.21, 7.31]</li> <li>1.27 [0.88, 1.84]</li> <li>2.71 [1.18, 6.24]</li> <li>1.64 [1.09, 2.47]</li> <li>3.02 [0.90, 10.09]</li> <li>1.63 [1.11, 2.40]</li> <li>4.22 [1.59, 11.20]</li> <li>1.64 [1.36, 1.99]</li> <li>25%</li> <li>3.33 [1.36, 8.15]</li> <li>2.94 [1.04, 8.32]</li> <li>2.05 [1.20, 3.50]</li> <li>1.50 [0.97, 2.32]</li> <li>1.95 [1.51, 2.51]</li> <li>%</li> <li>1.73 [1.48, 2.02]</li> <li>20%</li> </ul>   |          | Hazard                           | Ratio<br>m. 95% (     | CI        |        |
| B <u>Study</u><br>1.4.1<br>Zheng<br>Sesq<br>Sjöho<br>Winke<br>Guide<br>Zhou<br>Rojek<br>Gui 2<br>Voltin<br>Marct<br>Subto<br>Heter<br>Test f<br>1.4.2<br>Dean<br>Dean<br>Dean<br>Ligero<br>Galtie<br>Locke<br>Subto<br>Heter<br>Test f | tor Subdroub different<br>(y or Subgroup<br>Univariate<br>192 2020<br>192 2020<br>192 2021<br>192 2023<br>192 2023<br>192 2023<br>192 2023<br>192 2023<br>192 2023<br>192 2024<br>193   | Inces: Ch <sup>2</sup> = 1.07.<br>Iog[Hazard Ratio]<br>0.9439<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.9969<br>0.4947<br>1.1053<br>0.4886<br>1.4398<br>.02; Chi <sup>2</sup> = 12.06, d<br>= 5.07 (P < 0.0000<br>1.203<br>1.0784<br>0.6981<br>0.7178<br>0.4055<br>.00; Chi <sup>2</sup> = 3.40, df<br>= 5.18 (P < 0.0000<br>.02; Chi <sup>2</sup> = 17.39, d<br>= 6.93 (P < 0.0000 | at = 1 (P =           0.59679           0.19679           0.15846           0.45918           0.42568           0.20841           0.42568           0.49801           f = 9 (P = 0           1)           0.456678           0.27307           0.22355           = 4 (P = 0.1)           1) | 0.30).   <sup>2</sup> =<br>Weight<br>1.7%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>3.1%<br>10.3%<br>1.6%<br>11.1%<br>2.3%<br>70.4%<br>0.21);   <sup>2</sup> = 1<br>2.8%<br>2.1%<br>8.7%<br>6.8%<br>9.3%<br>29.6%<br>49);   <sup>2</sup> = 0'<br>100.0%<br>0.24);   <sup>2</sup> =     | Hazard Ratio<br>IV. Random. 95% Cl<br>2.57 [0.80, 8.28]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.71 [1.18, 6.24]<br>1.64 [1.09, 2.47]<br>3.02 [0.90, 10.09]<br>1.63 [1.11, 2.40]<br>4.22 [1.59, 11.20]<br>1.64 [1.36, 1.99]<br>25%<br>3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.95 [1.51, 2.51]<br>%<br>1.73 [1.48, 2.02]<br>20%  | N        | Hazard                           | Ratio<br>m. 95% (     | <u>cı</u> | -<br>- |

the subgroup analysis of the association between MTV at baseline and PFS of NFL patients after CAR-T therapy; (A), forest plots for the subgroup analysis according to the methods for determining the cutoff of MTV; and (B), forest plots for the subgroup analysis according to the analytic models.

Additionally, separate sub-analysis on the CAR-T product was not undertaken, which may also have an impact on the outcomes. For example, the study with the third generation CAR has been included in the analysis (29) and currently there is not strong evidence on how these products perform and their impact on outcomes, especially compared with the licensed second generation ones. Accordingly, future prospective studies with large sample size are still needed to determine whether previous lines of treatment may modify the association between MTV and survival outcomes of NHL patients after CAR-T therapy, and to explore the potential underlying mechanisms.

The strengths of this meta-analysis include its comprehensive literature search, rigorous inclusion criteria, and robust statistical analyses accounting for heterogeneity across studies. However, certain limitations should be acknowledged. First, 11 retrospective or *post-hoc* analysis was included in the meta-analysis, which may expose the results to the risk of recall and selection biases. However, subgroup analysis according to study design showed consistent

| Study or Subarcon  | log[Logord D-H-1   | e-   | Moinht  | IV Bandam 05% Cl   | N/ Dende      |   |
|--|--|--|---|--|---------------|---|
| - Study or Subgroup  | IUGEMAZARO KATIO   | <u>SE</u>  | weight  | iv, Random, 95% Cl   | iv, Kando     | m, 95% Cl                                 |
| 1.5.2 wealan of previo   | us lines of therapy  | = 2 or 3   | 0.00/   | 0.00.00.00.00.00   |               |   |
| Dean 2020 C1   | 1.203  | 0.45678  | 6.9%  | 3.33 [1.36, 8.15]  |               |   |
| Dean 2020 C2   | 1.0784   | 0.53078  | 5.4%  | 2.94 [1.04, 8.32]  |               |   |
| Galtier 2023   | 0.7178   | 0.27307  | 14.7%   | 2.05 [1.20, 3.50]  |               |   |
| Voltin 2024  | 0.4886   | 0.19777  | 20.9%   | 1.63 [1.11, 2.40]  |               |   |
| Marchal 2024   | 1.4398   | 0.49801  | 6.0%  | 4.22 [1.59, 11.20]   |               |   |
| Subtotal (95% CI)  |  |  | 54.0%   | 2.20 [1.58, 3.06]  |               | -   |
| Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z  | 0.03; Chi² = 5.03, df =<br>2 = 4.66 (P < 0.00001   | = 4 (P = 0.<br>I)  | .28); l² = 2  | 0%   |               |   |
| 1.5.3 Median of previo   | us lines of therapy  | = 4  |   |  |               |   |
| Sesques 2021   | 0.2311   | 0.19679  | 21.0%   | 1.26 [0.86, 1.85]  | +             | -   |
| Sjöholm 2022   | 0.392  | 0.15846  | 25.0%   | 1.48 [1.08, 2.02]  |               |   |
| Subtotal (95% CI)  |  |  | 46.0%   | 1.39 [1.09, 1.77]  |               | ◆   |
| Heterogeneity: Tau² = 0<br>Test for overall effect: Z  | 0.00; Chi² = 0.41, df =<br>2 = 2.66 (P = 0.008)  | = 1 (P = 0.  | .52); l² = 0  | %  |               |   |
| Total (95% CI)   |  |  | 100.0%  | 1.79 [1.38, 2.32]  |               | •   |
| Heterogeneity: Tau <sup>2</sup> = 0  | 0.05; Chi² = 10.09, df   | = 6 (P = 0   | 0.12); I <sup>2</sup> = 4   | 41%  |               |   |
| Test for overall effect: Z   | z = 4.39 (P < 0.0001)  |  |   |  | 0.1 0.2 0.5 1 | 2 5 10                                    |
| Test for subaroup differ   | ences: Chi² = 4.83. c  | if = 1 (P =  | 0.03). l² =   | 79.3%  |               |   |
|  |  |  |   |  |               | -   |
|  |  |  |   | Hazard Ratio   | Hazard        | Ratio                                     |
| Study or Subgroup  | log[Hazard Ratio]  | SE   | Weight  | IV, Random, 95% Cl   | IV, Rando     | m, 95% Cl                                 |
| 1.6.1 Not industry sup   | ported   |  |   |  |               |   |
| Zheng 2020   | 0.9439   | 0.59679  | 1.7%  | 2.57 [0.80, 8.28]  |               |   |
| Zhou 2023  | 0.9969   | 0.42568  | 3.1%  | 2.71 [1.18, 6.24]  |               |   |
| Gui 2024   | 1.1053   | 0.61567  | 1.6%  | 3.02 [0.90, 10.09]   |               |   |
| Marchal 2024   | 1.4398   | 0.49801  | 2.3%  | 4.22 [1.59, 11.20]   |               |   |
| Subtotal (95% CI)  |  |  | 8.7%  | 3.08 [1.86, 5.11]  |               |   |
| Heterogeneity: Tau <sup>2</sup> = 0  | ).00; Chi² = 0.58, df =  | = 3 (P = 0.  | .90); $I^2 = 0^4$   | %  |               |   |
|  | ' = 4 36 (P < 0.0001)  |  |   |  |               |   |
| Test for overall effect: Z   | . = 4.00 (1 < 0.0001)  |  |   |  |               |   |
| Test for overall effect: Z   | ed   |  |   |  |               |   |
| Test for overall effect: Z<br>1.6.2 Industry support<br>Dean 2020 C1   | red 1.203  | 0.45678  | 2.8%  | 3.33 [1.36, 8, 15]   |               | <u> </u>                                  |
| Test for overall effect: Z<br>1.6.2 Industry support<br>Dean 2020 C1<br>Dean 2020 C2   | red<br>1.203   | 0.45678  | 2.8%<br>2.1%  | 3.33 [1.36, 8.15]<br>2 94 [1 04, 8 32]   |               | <u> </u>                                  |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021  | red<br>1.203<br>1.0784<br>0 2311   | 0.45678<br>0.53078<br>0.19679  | 2.8%<br>2.1%<br>11.1%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86 1.85]   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Siöholm 2022  | red<br>1.203<br>1.0784<br>0.2311<br>0.392  | 0.45678<br>0.53078<br>0.19679<br>0.15846   | 2.8%<br>2.1%<br>11.1%<br>14 7%  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886  | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918  | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]  | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023  | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.23  | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816   | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Linero 2023   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335  | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.48]  | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtior 2023   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335<br>0.27307   | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]  | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335<br>0.27307<br>0.2255                                     | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Paioke 2024  | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4045   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335<br>0.27307<br>0.22355<br>0.20841                         | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]  | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltio 2024  | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4927   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335<br>0.27307<br>0.22355<br>0.20841                         | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltin 2024<br>Subtetal (25% C1)   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.18816<br>0.23335<br>0.27307<br>0.22355<br>0.20841<br>0.19777              | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>11.1%   | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]  | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltin 2024<br>Subtotal (95% CI)   | red<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.45918<br>0.23335<br>0.27307<br>0.22355<br>0.20841<br>0.19777              | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>11.1%<br>91.3%  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]<br>1.61 [1.40, 1.86]                                   | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltin 2024<br><b>Subtotal (95% CI)</b><br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z   | ed<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886<br>0.00; Chi <sup>2</sup> = 10.81, df<br>2 = 6.51 (P < 0.0000 <sup>-</sup>   | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.27335<br>0.27307<br>0.22355<br>0.20841<br>0.19777<br>= 10 (P =            | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>11.1%<br>91.3%<br>0.37); l <sup>2</sup> =                                       | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]<br>1.61 [1.40, 1.86]<br>* 8%                           | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltin 2024<br><b>Subtotal (95% CI)</b><br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z<br><b>Total (95% CI)</b>  | eed<br>1.203<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886<br>0.00; Chi <sup>2</sup> = 10.81, df<br>= 6.51 (P < 0.0000 <sup>-</sup> )  | 0.45678<br>0.53078<br>0.19679<br>0.45918<br>0.45918<br>0.23335<br>0.27307<br>0.22355<br>0.20841<br>0.19777<br>= 10 (P =            | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>10.3%<br>11.1%<br>91.3%<br>20.37); l <sup>2</sup> =                             | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]<br>1.61 [1.40, 1.86]<br>8%                             | -             | •<br>•<br>•<br>•<br>•<br>•<br>•<br>•<br>• |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Rojek 2024<br>Voltin 2024<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z<br><b>Total (95% CI)</b><br>Heterogeneity: Tau <sup>2</sup> = 0          | 2 4.00 (1 4 0.0001)<br>2 4.00 (1 4 0.0001)<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886<br>0.00; Chi <sup>2</sup> = 10.81, df<br>2 = 6.51 (P < 0.0000 <sup>-1</sup> )<br>0.02; Chi <sup>2</sup> = 17.39, df                                       | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.45918<br>0.23335<br>0.27307<br>0.22355<br>0.20841<br>0.19777<br>= 10 (P = | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>11.1%<br>91.3%<br>0.37); l <sup>2</sup> =<br>1000.0%<br>0.24); l <sup>2</sup> = | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]<br>1.61 [1.40, 1.86]<br>8 %                            | -             |   |
| Test for overall effect: Z<br><b>1.6.2 Industry support</b><br>Dean 2020 C1<br>Dean 2020 C2<br>Sesques 2021<br>Sjöholm 2022<br>Winkelmann 2022<br>Guidetti 2023<br>Ligero 2023<br>Galtier 2023<br>Locke 2024<br>Voltin 2024<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z<br>Total (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: Z | 2 4.00 (1 4 0.0001)<br>2 4.00 (1 4 0.0001)<br>1.0784<br>0.2311<br>0.392<br>1.0886<br>0.239<br>0.6981<br>0.7178<br>0.4055<br>0.4947<br>0.4886<br>0.00; Chi <sup>2</sup> = 10.81, df<br>2 = 6.51 (P < 0.0000 <sup>-</sup> )<br>0.02; Chi <sup>2</sup> = 17.39, df<br>2 = 6.93 (P < 0.0000 <sup>-</sup> ) | 0.45678<br>0.53078<br>0.19679<br>0.15846<br>0.45918<br>0.23335<br>0.27307<br>0.22355<br>0.20841<br>0.19777<br>= 10 (P =            | 2.8%<br>2.1%<br>11.1%<br>14.7%<br>2.7%<br>11.8%<br>8.7%<br>6.8%<br>9.3%<br>10.3%<br>11.1%<br>91.3%<br>0.37);   <sup>2</sup> =<br>100.0%<br>0.24);   <sup>2</sup> =  | 3.33 [1.36, 8.15]<br>2.94 [1.04, 8.32]<br>1.26 [0.86, 1.85]<br>1.48 [1.08, 2.02]<br>2.97 [1.21, 7.31]<br>1.27 [0.88, 1.84]<br>2.01 [1.27, 3.18]<br>2.05 [1.20, 3.50]<br>1.50 [0.97, 2.32]<br>1.64 [1.09, 2.47]<br>1.63 [1.11, 2.40]<br>1.61 [1.40, 1.86]<br>8%<br>1.73 [1.48, 2.02]<br>20% |               | •<br>•<br>•<br>•<br>2 5 10                |

Forest plots for the subgroup analysis of the association between MTV at baseline and PFS of NHL patients after CAR-T therapy; (A), forest plots for the subgroup analysis according to the median of previous lines of treatments; and (B), forest plots for the subgroup analysis according to whether the study was industry supported.

results. Second, 13 of the included studies enrolled patients with LBC, and the results of the meta-analysis were mostly driven by studies with patients of LBCL. The association between MTV and the survival of patients with other subtypes of NHL should still be investigated in the future. Third, moderately statistical heterogeneity was observed for the meta-analysis of the association between MTV and OS of NHL patients after CAR-T therapy, and the subgroup analysis results based on limited study-level data suggest that the number of previous treatment lines may

modulate the association. We were unable to determine the influence of patient physical status on the association between MTV and survival outcomes in a subgroup or meta-regression analysis because none of the included studies reported the outcome according to the class of ECOG PS, and on study-level, data of ECOG PS of the included studies were reported in a non-uniform manner. In addition, recent publications have correlated a high tumor burden (reflected by MTV) with a higher risk of infections, and the latter has been related with a higher non-relapse mortality

#### TABLE 6 Results of univariate meta-regression analysis.

| Variables                      | HR for PFS  |                     |          | HR for OS   |                     |          |
|--------------------------------|-------------|---------------------|----------|-------------|---------------------|----------|
|                                | Coefficient | 95% CI              | P values | Coefficient | 95% CI              | P values |
| Sample size                    | -0.00055    | -0.00475 to 0.00365 | 0.78     | -0.0012     | -0.0142 to 0.0118   | 0.84     |
| Mean age (years)               | 0.0071      | -0.0376 to 0.0519   | 0.74     | 0.00078     | -0.05747 to 0.05902 | 0.98     |
| Men (%)                        | 0.0061      | -0.0159 to 0.0282   | 0.56     | 0.022       | -0.022 to 0.066     | 0.29     |
| Cutoff of MTV (mL)             | 0.00034     | -0.00098 to 0.00166 | 0.59     | -0.00076    | -0.00368 to 0.00217 | 0.58     |
| Follow-up<br>duration (months) | -0.0025     | -0.0203 to.01534    | 0.77     | -0.023      | -0.053 to 0.006     | 0.10     |
| NOS                            | 0.035       | -0.126 to 0.196     | 0.65     | 0.078       | -0.214 to 0.371     | 0.57     |

HR, hazard ratio; PFS, progression-free survival; OS, overall survival; CI, confidence interval; MTV, metabolic tumor volume; NOS, Newcastle-Ottawa Scale.



Forest plots for the meta-analysis of the association between MTV at baseline and OS of NHL patients after CAR-T therapy; (A), forest plots for the overall meta-analysis; and (B), forest plots for the subgroup analysis according to study design.

| • | Study or Subgroup   | log[Hazard Ratio]   | SE  | Weight   | IV, Random, 95% CI   | IV, Ra   | ndom, 95% Cl                      |          |
|---|---|---|---|--|--|----------|-----------------------------------|----------|
|   | 2.3.1 Median  |   |   |  |  |          |                                   |          |
|   | Wang 2019   | 0.3001  | 0.45093   | 7.3%   | 1.35 [0.56, 3.27]  |          | - <b> -</b>                       |          |
|   | Dean 2020 C1  | 1.6094  | 0.5357  | 5.9%   | 5.00 [1.75, 14.29]   |          |                                   |          |
|   | Dean 2020 C2  | 1.7138  | 0.72636   | 3.8%   | 5.55 [1.34, 23.04]   |          |                                   |          |
|   | Zheng 2020  | 1.477   | 0.73127   | 3.8%   | 4.38 [1.04, 18.36]   |          | · · · · ·                         |          |
|   | Sjöholm 2022  | 0.239   | 0.1329  | 15.1%  | 1.27 [0.98, 1.65]  |          | -                                 |          |
|   | Winkelmann 2022   | 0.2546  | 0.55853   | 5.6%   | 1.29 [0.43, 3.85]  |          |                                   |          |
|   | Ligero 2023<br>Subtotal (95% CI)  | 0.3646  | 0.30487   | 10.5%<br><b>52.0%</b>  | 1.44 [0.79, 2.62]<br>1.86 [1.21, 2.87]   |          | •                                 |          |
|   | Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2   | 0.15; Chi² = 12.10, di<br>Z = 2.83 (P = 0.005)  | <sup>:</sup> = 6 (P = 0   | 0.06); l <sup>2</sup> =  | 50%  |          |                                   |          |
|   | 2.3.2 ROC curve anal  | vsis derived  |   |  |  |          |                                   |          |
|   | Galtier 2023  | 1.5085  | 0.29989   | 10.6%  | 4.52 [2.51, 8.14]  |          | _ <b>_</b>                        |          |
|   | Zhou 2023   | 1 2149  | 0.50529   | 6.4%   | 3 37 [1 25 9 07]   |          |                                   |          |
|   | Rojek 2024  | 0.5653  | 0.21867   | 12.9%  | 1.76 [1.15, 2.70]  |          |                                   |          |
|   | Gui 2024  | 3.3607  | 3.26549   | 0.2%   | 28.81 [0.05, 17342.97]   |          |                                   | <b>→</b> |
|   | Voltin 2024   | 0.3365  | 0.24949   | 12.0%  | 1.40 [0.86. 2.28]  |          | + <b>-</b> -                      |          |
|   | Marchal 2024  | 1.0152  | 0.53341   | 5.9%   | 2.76 [0.97, 7.85]  |          |                                   |          |
|   | Subtotal (95% CI)   |   | 0.00011   | 48.0%  | 2.40 [1.51, 3.81]  |          | •                                 |          |
|   | Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2   | 0.16; Chi² = 11.57, di<br>Z = 3.70 (P = 0.0002  | <sup>:</sup> = 5 (P = (<br>)  | 0.04); l² =  | 57%  |          |                                   |          |
|   | Total (95% CI)  |   |   | 100.0%   | 2.11 [1.54, 2.89]  |          | •                                 |          |
|   | Heterogeneity: Tau <sup>2</sup> = (   | 0.15; Chi² = 28.67, d   | i = 12 (P =   | : 0.004); l²   | ² = 58%  |          |                                   | 50       |
|   | Test for overall effect: 7  | Z = 4.62 (P < 0.0000  | 1)  |  |  | 0.02 0.1 | 1 10                              | 50       |
|   | Test for subaroup diffe   | rences: Chi <sup>2</sup> = 0.61.  | df = 1 (P =   | : 0.43).  ² :  | = 0%   |          |                                   |          |
|   |   |   |   |  |  |          |                                   |          |
| 2 |   |   |   |  | Hazard Ratio   | Ha       | zard Ratio                        |          |
| _ | Study or Subgroup   | log[Hazard Ratio]   | SE  | Weight   | IV, Random, 95% CI   | IV, Ra   | ndom, 95% Cl                      |          |
|   | 2.4.1 Univariate  |   |   |  |  |          |                                   |          |
|   | Wang 2019   | 0.3001  | 0.45093   | 7.3%   | 1.35 [0.56, 3.27]  |          | - <b> -</b>                       |          |
|   | Zheng 2020  | 1.477   | 0.73127   | 3.8%   | 4.38 [1.04, 18.36]   |          |                                   |          |
|   | Sjöholm 2022  | 0.239   | 0.1329  | 15.1%  | 1.27 [0.98, 1.65]  |          | •                                 |          |
|   | Winkelmann 2022   | 0.2546  | 0.55853   | 5.6%   | 1.29 [0.43, 3.85]  |          |                                   |          |
|   | Zhou 2023   | 1.2149  | 0.50529   | 6.4%   | 3.37 [1.25, 9.07]  |          |                                   |          |
|   |   |   | 0 21867   | 12 0%  |  |          | - <b>-</b> -                      |          |
|   | Rojek 2024  | 0.5653  | 0.21001   | 12.370   | 1.76 [1.15, 2.70]  |          |                                   |          |
|   | Rojek 2024<br>Gui 2024  | 0.5653<br>3.3607  | 3.26549   | 0.2%   | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]  |          |                                   | -        |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024   | 0.5653<br>3.3607<br>0.3365  | 3.26549<br>0.24949  | 0.2%<br>12.0%  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]   |          |                                   | _        |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024   | 0.5653<br>3.3607<br>0.3365<br>1.0152  | 3.26549<br>0.24949<br>0.53341   | 0.2%<br>12.0%<br>5.9%  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]  |          |                                   | _        |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% CI)  | 0.5653<br>3.3607<br>0.3365<br>1.0152  | 3.26549<br>0.24949<br>0.53341   | 0.2%<br>12.0%<br>5.9%<br><b>69.1%</b>  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br><b>1.56 [1.24, 1.95]</b>  |          | •                                 | _        |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2   | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001   | 3.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.  | 0.2%<br>12.0%<br>5.9%<br><b>69.1%</b><br>.33); l <sup>2</sup> = 1  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%   |          | •                                 |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate   | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi² = 9.14, df<br>Z = 3.86 (P = 0.0001)  | 3.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.  | 0.2%<br>12.0%<br>5.9%<br><b>69.1%</b><br>.33); I <sup>2</sup> = 1  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%   |          | •                                 |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1   | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001)<br>1.6094  | 3.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.)   | 0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); I <sup>2</sup> = 1   | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%   |          | •<br>•                            | -        |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2   | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001)<br>1.6094<br>1.7138  | 3.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.)<br>0.5357<br>0.72636  | 0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%   | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br><b>1.56 [1.24, 1.95]</b><br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]  |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = 1<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023  | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001)<br>1.6094<br>1.7138<br>0.3646  | 3.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.)<br>0.5357<br>0.72636<br>0.30487   | 0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]  |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023  | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001)<br>1.6094<br>1.7138<br>0.3646<br>1.5085  | 0.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.)<br>0.5357<br>0.72636<br>0.30487<br>0.29989  | 12:378<br>0.2%<br>12:0%<br>5.9%<br><b>69:1%</b><br>.33); I <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]   |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023<br>Subtotal (95% Cl)   | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi <sup>2</sup> = 9.14, df<br>Z = 3.86 (P = 0.0001<br>1.6094<br>1.7138<br>0.3646<br>1.5085   | 0.26549<br>0.24949<br>0.53341<br>= 8 (P = 0.)<br>0.5357<br>0.72636<br>0.30487<br>0.29989  | 12.3 %<br>0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%<br><b>30.9%</b>   | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]<br>3.34 [1.61, 6.93]  |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2  | $\begin{array}{c} 0.5653\\ 3.3607\\ 0.3365\\ 1.0152\\ \end{array}$ $\begin{array}{c} 0.02; \ \mathrm{Chi^2}=9.14, \ \mathrm{df}\\ \mathrm{Z}=3.86 \ (\mathrm{P}=0.0001\\ 1.6094\\ 1.7138\\ 0.3646\\ 1.5085\\ \end{array}$ $\begin{array}{c} 0.35; \ \mathrm{Chi^2}=9.29, \ \mathrm{df}\\ \mathrm{Z}=3.24 \ (\mathrm{P}=0.001) \end{array}$  | 0.5357<br>0.5357<br>0.72636<br>0.30487<br>0.72636<br>0.30487<br>0.29989<br>= 3 (P = 0.  | 0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%<br><b>30.9%</b><br>03); l <sup>2</sup> = 6  | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]<br>3.34 [1.61, 6.93]<br>8%  |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Marchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = 1<br>Test for overall effect: $2$<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = 0<br>Test for overall effect: $2$<br>Total (95% Cl)  | 0.5653<br>3.3607<br>0.3365<br>1.0152<br>0.02; Chi² = 9.14, df<br>Z = 3.86 (P = 0.0001<br>1.6094<br>1.7138<br>0.3646<br>1.5085<br>0.35; Chi² = 9.29, df :<br>Z = 3.24 (P = 0.001)  | 0.5357<br>0.5357<br>0.5357<br>0.72636<br>0.30487<br>0.29989<br>= 3 (P = 0.  | 12.3%<br>0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%<br>30.9%<br>.03); l <sup>2</sup> = 6                                     | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]<br>3.34 [1.61, 6.93]<br>8%  |          | •<br>•                            |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Warchal 2024<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: $2$<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023<br>Galtier 2023<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Total (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Total (95% Cl)   | $\begin{array}{c} 0.5653\\ 3.3607\\ 0.3365\\ 1.0152\\ \end{array}$ $\begin{array}{c} 0.02; \ Chi^2 = 9.14, \ df\\ Z = 3.86 \ (P = 0.0001\\ \end{array}$ $\begin{array}{c} 1.6094\\ 1.7138\\ 0.3646\\ 1.5085\\ \end{array}$ $\begin{array}{c} 0.35; \ Chi^2 = 9.29, \ df\\ Z = 3.24 \ (P = 0.001)\\ \end{array}$ $\begin{array}{c} 0.15; \ Chi^2 = 28.67, \ dt\\ Z = 4.62 \ (P < 0.0000\\ \end{array}$   | 0.5357<br>0.5357<br>0.72636<br>0.30487<br>0.29989<br>= 3 (P = 0.  | 12.3%<br>0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%<br><b>30.9%</b><br>.03); l <sup>2</sup> = 6<br><b>100.0%</b>             | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]<br>3.34 [1.61, 6.93]<br>8%<br>2.11 [1.54, 2.89]<br>2 = 58%            | 0.02 0.1 | •<br>•<br>•<br>•                  |          |
|   | Rojek 2024<br>Gui 2024<br>Voltin 2024<br>Voltin 2024<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>2.4.2 Multivariate<br>Dean 2020 C1<br>Dean 2020 C2<br>Ligero 2023<br>Galtier 2023<br>Galtier 2023<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Total (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Total (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>Test for subaroup differt: 2 | $\begin{array}{c} 0.6653\\ 3.3607\\ 0.3365\\ 1.0152\\ \end{array}$ $\begin{array}{c} 0.02; \mbox{ Chi}^2 = 9.14, \mbox{ df}\\ Z = 3.86 \ (P = 0.0001\\ \end{array}$ $\begin{array}{c} 1.6094\\ 1.7138\\ 0.3646\\ 1.5085\\ \end{array}$ $\begin{array}{c} 0.35; \mbox{ Chi}^2 = 9.29, \mbox{ df}\\ Z = 3.24 \ (P = 0.001)\\ \end{array}$ $\begin{array}{c} 0.15; \mbox{ Chi}^2 = 28.67, \mbox{ df}\\ Z = 4.62 \ (P < 0.0000\\ \mbox{ rences: \mbox{ Chi}^2 = 3.84, \mbox{ df}\\ \end{array}$ | 0.24949<br>0.24949<br>0.53341<br>= 8 (P = 0.)<br>0.5357<br>0.72636<br>0.30487<br>0.29989<br>= 3 (P = 0.)<br>= 12 (P = 1)<br>if = 1 (P = | 12.0%<br>0.2%<br>12.0%<br>5.9%<br>69.1%<br>.33); l <sup>2</sup> = 1<br>5.9%<br>3.8%<br>10.5%<br>10.6%<br>30.9%<br>.03); l <sup>2</sup> = 6<br>100.0%<br>0.004); l <sup>2</sup> | 1.76 [1.15, 2.70]<br>28.81 [0.05, 17342.97]<br>1.40 [0.86, 2.28]<br>2.76 [0.97, 7.85]<br>1.56 [1.24, 1.95]<br>3%<br>5.00 [1.75, 14.29]<br>5.55 [1.34, 23.04]<br>1.44 [0.79, 2.62]<br>4.52 [2.51, 8.14]<br>3.34 [1.61, 6.93]<br>8%<br>2.11 [1.54, 2.89]<br>2 = 58%<br>= 73.9% |          | <ul> <li>1</li> <li>10</li> </ul> |          |

analytic models.

in the long-term which may impact the survival outcomes (12, 47). However, only one of the included studies reported the incidence of infection of the included patients (38). Future studies are needed to determine if the incidence of infection after CAR-T may modify the association between MTV and survival outcomes of patients with NHL. Finally, the univariate-regression analysis was used in 11 of the included studies. Although a consistent result was observed in

subgroup analysis of multivariate analysis, we could not exclude the possibility that residual unadjusted factors may confound the association between a high baseline MTV and poor survival of NHL patients after CAR-T therapy.

MTV offers several advantages in the assessment of NHL patients undergoing CAR-T therapy. Firstly, it provides a quantitative measure of tumor burden, enabling a comprehensive evaluation beyond

Hazard Ratio Hazard Ratio IV. Random, 95% CI Study or Subgroup log[Hazard Ratio] SE Weight IV. Random, 95% CI 2.5.2 Median of previous lines of therapy = 2 or 3 Dean 2020 C1 1.6094 0.5357 11.3% 5.00 [1.75, 14.29] Dean 2020 C2 1.7138 8.0% 5.55 [1.34, 23.04] 0.72636 Galtier 2023 17.0% 4.52 [2.51, 8.14] 1.5085 0.29989 Voltin 2024 0.3365 0.24949 18.3% 1.40 [0.86, 2.28] Marchal 2024 1.0152 0.53341 11.3% 2.76 [0.97, 7.85] Subtotal (95% CI) 65.9% 3.15 [1.66, 5.97] Heterogeneity: Tau<sup>2</sup> = 0.33; Chi<sup>2</sup> = 12.15, df = 4 (P = 0.02); l<sup>2</sup> = 67% Test for overall effect: Z = 3.50 (P = 0.0005) 2.5.3 Median of previous lines of therapy = 4 Wang 2019 0.3001 0.45093 13.1% 1.35 [0.56, 3.27] Sjöholm 2022 0.239 0.1329 21.0% 1.27 [0.98, 1.65] Subtotal (95% CI) 34.1% 1.28 [0.99, 1.64] Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.02, df = 1 (P = 0.90); I<sup>2</sup> = 0% Test for overall effect: Z = 1.91 (P = 0.06) Total (95% CI) 100.0% 2.32 [1.40, 3.83] Heterogeneity: Tau<sup>2</sup> = 0.30; Chi<sup>2</sup> = 23.80, df = 6 (P = 0.0006); l<sup>2</sup> = 75% 0.02 0.1 10 50 Test for overall effect: Z = 3.28 (P = 0.001) Test for subgroup differences:  $Chi^2 = 6.61$ , df = 1 (P = 0.01),  $l^2 = 84.9\%$ Hazard Ratio Hazard Ratio В Study or Subgroup log[Hazard Ratio] IV. Random, 95% CI IV. Random, 95% Cl SE Weight 2.6.1 Not industry supported Wang 2019 0.3001 0.45093 7.3% 1.35 [0.56, 3.27] Zheng 2020 1.477 0.73127 3.8% 4.38 [1.04, 18.36] Zhou 2023 1.2149 0.50529 6.4% 3.37 [1.25, 9.07] Gui 2024 0.2% 3.3607 3,26549 28.81 [0.05, 17342.97] Marchal 2024 1.0152 0.53341 5.9% 2.76 [0.97, 7.85] Subtotal (95% CI) 23.6% 2.46 [1.46, 4.13] Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 3.40, df = 4 (P = 0.49); I<sup>2</sup> = 0% Test for overall effect: Z = 3.40 (P = 0.0007) 2.6.2 Industry supported Dean 2020 C1 1.6094 0.5357 5.9% 5.00 [1.75, 14.29] Dean 2020 C2 1.7138 0.72636 3.8% 5.55 [1.34, 23.04] Sjöholm 2022 1.27 [0.98, 1.65] 0.239 0.1329 15.1% Winkelmann 2022 0.2546 0.55853 5.6% 1.29 [0.43, 3.85] 1.44 [0.79, 2.62] Ligero 2023 0.3646 0.30487 10.5% 1.5085 0.29989 4.52 [2.51, 8.14] Galtier 2023 10.6% Rojek 2024 0 5653 0 21867 12.9% 1.76 [1.15, 2.70] Voltin 2024 0.3365 0.24949 12.0% 1.40 [0.86, 2.28] Subtotal (95% CI) 76.4% 2.00 [1.37, 2.92] Heterogeneity: Tau<sup>2</sup> = 0.18; Chi<sup>2</sup> = 23.15, df = 7 (P = 0.002); l<sup>2</sup> = 70% Test for overall effect: Z = 3.58 (P = 0.0003) Total (95% CI) 100.0% 2.11 [1.54. 2.89] Heterogeneity: Tau<sup>2</sup> = 0.15; Chi<sup>2</sup> = 28.67, df = 12 (P = 0.004); I<sup>2</sup> = 58% 0.02 0.1 10 50 Test for overall effect: Z = 4.62 (P < 0.00001) Test for subaroup differences:  $Chi^2 = 0.40$ . df = 1 (P = 0.53). I<sup>2</sup> = 0% FIGURE 7 Forest plots for the subgroup analysis of the association between MTV at baseline and OS of NHL patients after CAR-T therapy; (A), forest plots for

the subgroup analysis according to the median of previous lines of treatments; and (B), forest plots for the subgroup analysis according to whether the study was industry supported.

conventional anatomical imaging modalities. This quantitative assessment facilitates early detection of disease progression or response to therapy, guiding timely adjustments in treatment strategies. Additionally, high baseline MTV serves as a prognostic biomarker, aiding in risk stratification and identification of patients at higher risk of treatment failure or disease relapse. Despite its potential advantages, the measurement of MTV presents several methodological challenges that need to be addressed (48, 49). Variability in PET imaging protocols, including tracer dose and uptake time, can impact the accuracy and reproducibility of MTV measurements (48). Standardization of imaging protocols across institutions is crucial to

ensure consistency and comparability of MTV values. Furthermore, accurate delineation of tumor boundaries on PET images is challenging, particularly in cases of diffuse or heterogeneous disease involvement (48, 49). Standardized segmentation algorithms and quality assurance measures are needed to improve reproducibility. Moreover, PET/CT fusion artifacts and optimal thresholding methods for defining metabolically active tumor voxels pose additional challenges to MTV measurement (48). Advanced image registration techniques and standardized thresholding algorithms are required to mitigate artifacts and improve the reliability of MTV quantification (48). Despite these challenges, addressing methodological



considerations in MTV measurement will enhance its utility as a prognostic biomarker and guide clinical decision-making in the management of NHL patients undergoing CAR-T therapy.

From a clinical perspective, the identification of high MTV as a predictor of poor survival outcomes in NHL patients treated with CAR-T therapy has important implications for risk stratification, treatment selection, and patient management. Incorporating MTV assessment into routine clinical practice may facilitate personalized treatment approaches, such as intensification of therapy or consideration of alternative treatment strategies in patients with high-risk disease. Furthermore, future studies should focus on validating these findings in prospective cohorts, elucidating the biological mechanisms underlying the association between MTV and survival, and exploring therapeutic strategies to overcome treatment resistance in high-MTV tumors.

## Conclusions

In conclusion, this meta-analysis provides pilot evidence for the prognostic significance of MTV in NHL patients undergoing CAR-T therapy. Higher baseline MTV is consistently associated with poorer survival outcomes, highlighting its potential utility as a predictive biomarker for risk stratification and treatment optimization in this patient population. Further research efforts are warranted to validate these findings, elucidate underlying mechanisms, and translate these insights into clinical practice to improve outcomes for NHL patients undergoing CAR-T therapy.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

## Author contributions

LL: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. FJ: Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. HF: Conceptualization, Formal analysis, Funding acquisition, Resources, Software, Supervision, Validation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1433012/ full#supplementary-material

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