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REVIEW

Prognostic significance of [^{18}F]FDG PET metabolic parameters in adults and children with soft-tissue sarcoma: a meta-analysis

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Abstract

Background Soft-tissue sarcomas (STS) represent a diverse group of rare malignancies, underscoring the need for precise risk stratification. [^{18}F]fluoro-2-deoxy-2-d-glucose positron emission tomography ([^{18}F]FDG PET) imaging parameters have been proposed as potential prognostic indicators in several cancer types, yet their significance in STS remains under investigation. This study aimed to synthesize the available evidence and assess the prognostic value of these parameters.

Methods A systematic review and meta-analysis was conducted, employing a comprehensive literature search across multiple databases. The prognostic value of [^{18}F]FDG PET parameters, including pre- and post- treatment standardized uptake values (SUV1, SUV2), pretreatment metabolic tumor volume (MTV1) and total lesion glycolysis (TLG1) on event-free survival (EFS) and overall survival (OS) in patients with STS was examined.

Results Thirty-one studies with 1,932 patients were identified. The analyses demonstrated significant relationships between higher SUV1 (hazard ratio, HR 1.68 for EFS and 3.07 for OS, $p<0.001$), SUV2 (HR 3.13 for EFS and 2.09 for OS, $p<0.001$ and $p=0.001$ respectively), MTV1 (HR 2.29 for EFS and 3.05 for OS, $p=0.011$ and $p<0.001$ respectively), TLG1 (HR 2.85 for EFS and 3.23 for OS, $p=0.032$ and $p=0.002$ respectively) and poorer survival outcomes. However, the association of these parameters with survival outcomes was non-significant in pediatric patients.

Conclusion This study suggests that [^{18}F]FDG PET parameters could serve as important prognostic markers in adults with STS, but not in pediatric patients. Future studies with larger cohorts and uniform methodologies are critical to confirm and build upon these findings.

Keywords [^{18}F]FDG PET · Soft-tissue sarcomas · Rhabdomyosarcoma · SUVmax · MTV · TLG

Abbreviations

[^{18}F]FDG	[^{18}F]fluoro-2-deoxy-2-d-glucose
CI	Confidence interval
EFS	Event-free survival
FNCLCC	Fédération Nationale des Centres de Lutte Contre Le Cancer Sarcoma Group
HR	Hazard ratio
IQR	Interquartile range
M	Multicenter
Me	Median
MTV	Metabolic tumor volume
NA	Not applicable
NAC	Neoadjuvant chemotherapy
NR	Not reported
OS	Overall survival
PET	Positron emission tomography
Pro	Prospective
Prov	Provided
REML	REstricted Maximum–Likelihood
Retro	Retrospective
RMS	Rhabdomyosarcoma
ROC	Receiver operating characteristic curve
S	Single center
SD	Standard deviation
STS	Soft-tissue sarcoma
SUV	Standardized uptake value

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TLG	Total lesion glycolysis
TSA	Trial sequential analysis

Introduction

Soft-tissue sarcomas (STS) are rare tumors that present challenges in cancer management due to their diverse biological characteristics and clinical presentations, which are primarily associated with their origin from mesenchymal cells [1, 2]. Representing approximately 1% of malignancies in adults and 8–15% in children, adolescents, and young adults [3, 4], the complexity of STS challenges diagnosis, treatment planning and prognostic evaluation [5–7]. Despite progressive strides in surgical techniques, radiation oncology, and systemic therapies, the prognosis for patients with STS remains unsatisfactory, emphasizing the urgent necessity for enhanced prognostic markers and therapeutic strategies [8].

Traditional prognostic factors, including patient age, presence of metastasis, tumor size, histological type, and tumor grade, guide clinical decision-making in oncology [9, 10]. However, these factors have limited efficacy in accurately predicting patient outcomes, thereby highlighting the compelling need for the development and validation of more reliable and accurate prognostic tools. A reliable prognostic tool in soft-tissue sarcomas may enhance patient management by allowing for the customization of treatment strategies, such as precise surgical techniques, individualized systemic therapies, and patient-oriented follow-up schedules, thereby improving treatment outcomes and patient quality of life.

The pivotal role of [^{18}F]fluoro-2-deoxy-2-d-glucose positron emission tomography ([^{18}F]FDG PET) in oncology has been well-established, and is recognized for its substantial contribution to tumor staging and grading, monitoring treatment efficacy, detecting local or distant recurrence, and facilitating post-treatment follow-up management [11]. Despite this, the ability of [^{18}F]FDG PET parameters to predict survival outcomes in patients with sarcoma remains a subject of debate, as research has presented both supportive and contradictory findings [12–16]. Prior meta-analyses have examined the prognostic value of [^{18}F]FDG PET parameters in patients with sarcoma [17–19], but recent research indicates a potentially diminished prognostic efficacy of these parameters in the pediatric population [19–21]. Importantly, previous meta-analyses failed to consider the pediatric population separately, thereby potentially obscuring the true prognostic value of [^{18}F]FDG PET parameters due to known biological and clinical differences between pediatric and adult sarcomas and among different sarcoma subtypes [3, 7].

To address this gap, we performed a systematic review and meta-analysis that incorporates an in-depth analysis of age subgroups and sensitivity analyses to comprehensively evaluate the relationship between [^{18}F]FDG PET metabolic parameters and survival outcomes in patients with STS.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The study protocol was registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) under the registration number INPLASY202370087 (https://doi.org/10.37766/inplasy2023.7.0087).

Search strategy

A systematic literature search of studies published within the last 15 years (from Jan 1, 2008 to June 1, 2023, date of search: June 15, 2023) was performed in Medline, PubMed, Google Scholar, and the Cochrane Library by two independent investigators (MY and LB). The search methodology utilized Medical Subject Headings (MeSH). Both backward and forward snowballing methods were also used for an exhaustive search. Language restrictions were not applied.

The detailed search strategy and queries are available in the supplemental material (Supplemental Appendix 1).

Eligibility criteria and study selection

After automatic removal of duplicate records, the remaining studies were screened by two independent researchers (MY and YL) for eligibility. We considered studies that met the following criteria:

1. *Population*: children, adolescents and adults with STS undergoing baseline and/or post-neoadjuvant chemotherapy (NAC) PET/CT with [^{18}F]FDG;
2. *Exposure*: high baseline/post-NAC maximum standardized uptake value (SUVmax), high SUV ratio (SUV2 [post-NAC] / SUV1 [baseline]), high baseline metabolic tumor volume (MTV1), high baseline total lesion glycolysis (TLG1) values;
3. *Comparator*: low baseline/post-NAC SUVmax, low SUV ratio, low baseline MTV1, low baseline TLG1 values;
4. *Outcomes*: event-free survival (EFS), overall survival (OS);
5. *Study design*: prospective and retrospective cohort studies.
6. The full text of potentially eligible studies was assessed by applying the inclusion and exclusion criteria.

The inclusion criteria for this study were: cohort studies involving patients diagnosed with STS, specifically investigating the association between [^{18}F]FDG PET metabolic parameters (SUVmax, MTV, or TLG) and survival outcomes (OS or EFS).

Studies were excluded if they met one or more of the following criteria: (1) review articles, case reports; (2) other tumors (bone sarcomas, Ewing's sarcomas); (3) no relevant outcomes; (4) animal studies; (5) outcomes reported for mixed groups (bone sarcomas and STS); (6) other radiopharmaceuticals used; (7) duplicated publications.

Any divergences were resolved through consensus, with the supervising researcher (YL) stepping in when necessary.

Data extraction

A dedicated data collection form was developed for this review, which two authors (MY and LB) used to independently assess the complete manuscripts of all included trials and extract the data. Extracted information encompassed: (1) Basic study details such as the first author, publication year, country, journal, study design, period, the number of centers involved, follow-up period, and sample size; (2) [^{18}F]FDG PET scan data like PET scanners used, fasting duration, pre-injection blood glucose tests, post-injection interval, [^{18}F]FDG dose, and PET/CT timing; (3) Patient and tumor specifics including cancer type, disease stage, histological grade (using the Fédération Nationale des Centres de Lutte Contre Le Cancer [FNCLCC] grading system if applicable [23]), tumor location, patient age and sex; (4) [^{18}F]FDG PET parameters such as MTV and TLG segmentation methods, SUV type, cut-off determination method and values, and effect estimates for study outcomes. We also examined the supplementary or additional files associated with the included articles for any pertinent data.

SUV1 and SUV2 were defined as the SUV of the primary lesion pre- and post- NAC, respectively. The SUV ratio was calculated as SUV2/SUV1. TLG1 and MTV1 values were extracted from baseline [^{18}F]FDG PET scans.

Outcome measures such as OS, EFS, Kaplan–Meier curves, and hazard ratio (HR) values were extracted. For the purpose of this meta-analysis, we consolidated progression-free survival, disease-free survival, metastasis-free survival, and event-free survival from the included studies, collectively defining them as EFS.

HR values were used to measure the association between [^{18}F]FDG PET metabolic parameters and survival. Univariate HR values were extracted directly if available or calculated using Tierney et al. methodology for original studies [24], univariate HR were replaced with multivariable if available. This involved gathering relevant data, including p values from the log-rank test, the total count of patients in each group, and the number of events, allowing us to calculate univariate HRs indirectly. Direct HR extraction was performed from provided survival curves when present.

Data analysis and synthesis

We used STATA 17 (StataCorp LLC, Texas, US) and Cochrane tool Review Manager (RevMan version 5.3) to perform meta-analysis.

The impact of [^{18}F]FDG PET parameters on survival outcomes was assessed by calculating the pooled HR values with its 95% confidential intervals (CIs).

Inter-study heterogeneity was evaluated using the I-squared (I^2) statistic and the Cochrane Q test, as recommended by the Cochrane Handbook [25]. If the value was $\geq 40\%$ and/or $p < 0.05$, an effect estimate was considered as significant for heterogeneity and random-effects model (restricted maximum–likelihood, REML) was used. Otherwise, a fixed-effects model based on the inverse-variance approach was used. Results of meta-analysis were presented using forest-plots. Statistical significance was set at 0.05 for hypothesis testing.

We conducted a meta-regression analysis, leveraging the REML random-effects model, to ascertain if the relationships between SUV1 and survival outcomes might be affected by variables such as patient age, sex, histological grade, tumor location and stage, cut-off value, and the design of the study [26]. The results of the meta-regression were graphically represented using bubble-plots. The correlation between clinical parameters of eligible studies was evaluated using Spearman's rank correlation coefficient.

Trial sequential analysis (TSA) was applied to examine the sufficiency and currently available evidence. TSA was conducted for survival outcomes and SUV1 parameter, which is supported by the most substantial evidence. The analysis was carried out utilizing dedicated TSA software (Trial Sequential Analysis (TSA) [Computer program]. Version 0.9.5.10 Beta. The Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital—Rigshospitalet, 2021). If the cumulative Z-curve crosses the monitoring boundaries, it suggests that sufficient evidence for the association between high SUV1 values (exposure) and the survival outcome may have been reached, indicating that further studies may not be needed [27]. The type I error rate was maintained at 5% ($\alpha = 0.05$), and required heterogeneity adjusted information sizes were calculated with 90% power ($\beta = 0.10$), relative risk reduction was set at 30%.

Internal validity and risk of bias assessment

The internal validity and risk of bias were assessed by two independent reviewers (MY, LB) using the "Tool to assess risk of bias in cohort studies" contributed by the CLARITY

Group at McMaster University [28], the explanation for risk of bias assessment is presented in Supplemental Appendix 2. Eight areas were evaluated: patient selection, exposure assessment, pre-existing exposure, control matching, confounding assessment, measurement of the outcome, follow-up assessment, and co-intervention assessment. The risk of bias was rated as low, moderate, or high. The results were presented using the "Risk-of-Bias Visualization tool" [29].

Publication bias and small-study effects were assessed using Egger's test and funnel plot analysis [30]. We also used a GRADE systematic approach to rate the certainty of evidence. Baseline evidence level was high as for studies of prognostic factor [31].

Sensitivity analysis

We conducted a sensitivity analysis in several ways: Firstly, we analyzed the multivariable HRs obtained from the Cox multivariable regression analysis in the original studies.

Secondly, we separately examined studies focusing on pediatric and adult patients with STS. Pediatric patients were defined per the Food and Drug Administration (FDA) guidelines, which classify the pediatric population as birth through 21 years of age [32]. The patient populations in the majority of the eligible studies consisted of a diverse mix of both adults and children, in varying proportions. To clearly categorize the studies based on patient demographics, we employed a strategy wherein studies were classified as 'pediatric' if they comprised 75% or more pediatric patients. Conversely, studies were labeled as 'adult' if pediatric patients made up less than 25% of the study population.

Finally, we evaluated the results of studies with only low-to-moderate overall risk of bias.

Results

Baseline characteristics of the included studies

The initial literature search yielded a total of 6,775 studies across multiple databases, and an additional 41 studies were obtained through other sources (Fig. 1).

Following the removal of duplicate and irrelevant records, the remaining 1,495 articles underwent title and abstract screening. From these, 147 full-text articles were reviewed for eligibility criteria. A total of 1932 patients from 31 studies were included in this systematic review and meta-analysis [12–15, 20, 33–58] with major exclusions presented in Supplemental Table 1.

The characteristics of the included studies are shown in Table 1.

Among the 31 included studies, four were prospective observational [45, 46, 52, 55]; six studies [14, 42, 43, 45, 50, 52] were designed as multicentric, and the remaining studies followed a single-center design. The mean age of the patients within included studies ranged between 5 to 74 years, and six studies were designated as 'pediatric' [12, 13, 39, 41, 42, 45]. The included studies varied in aspects of metastatic disease stage, tumor location, and histological grade. The distribution of soft-tissue sarcoma types across the included studies can be found in Supplemental Table 2. Notably, all studies classified as 'pediatric' incorporated patients diagnosed with rhabdomyosarcomas (RMS), with a similar distribution in RMS subtypes (embryonal, alveolar).

Table 2 outlines the different methodologies of [^{18}F]FDG PET scanning employed across the studies.

The scanning protocols administered were not uniform and varied according to the individual study design. Likewise, there was a lack of consistency in the methods used to determine the cut-off values across the studies. Sixteen studies leveraged receiver operating characteristic (ROC) curves, seven utilized median values, two applied cut-off point analyses, two others relied on the minimal p value method, and one referred to previous research for their cut-off. A comprehensive summary of the cut-off values employed in the eligible studies can be found in Supplemental Table 3. Two studies used SUVpeak [43, 46] and one study used SUVmean [20] instead of SUVmax. For MTV and TLG calculation, six studies applied a fixed absolute segmentation method (SUV 2–2.5) [36–38, 44, 50, 51], and three studies used a fixed relative threshold of 40% [34, 40, 42].

Prognostic value of [^{18}F]FDG PET parameters for EFS and OS

SUV1: In a meta-analysis of 16 studies involving 1222 patients, we found a significant association between SUV1 and EFS (HR = 1.68, p < 0.001, high heterogeneity: $I^2 = 94\%$; Fig. 2; Supplemental Fig. 2, Table 3).

This relationship was confirmed in multivariable data analysis (HR = 1.75, $p = 0.025$) and in the subgroup analysis of low-to-moderate bias studies (HR = 1.82, $p = 0.004$). 'Adult' studies ($n = 610$) exhibited a stronger correlation (HR = 2.49, $p < 0.001$, $I^2 = 0$), whereas 'pediatric' studies ($n = 517$) found no significant association (HR = 1.14, $p = 0.2$, Fig. 3).

The correlation of SUV1 with OS, as confirmed by 22 studies encompassing 1,312 patients, was significant (HR = 3.07, $p < 0.001$, high heterogeneity: $I^2 = 74\%$; Fig. 2; Supplemental Fig. 2, Table 3). This outcome was validated by subgroup analyses based on the statistical analysis method (HR = 2.84, $p = 0.002$), as well as by the subgroup analysis of low-to-moderate bias studies (HR = 2.94, $p < 0.001$). This association was more pronounced in 'adult'

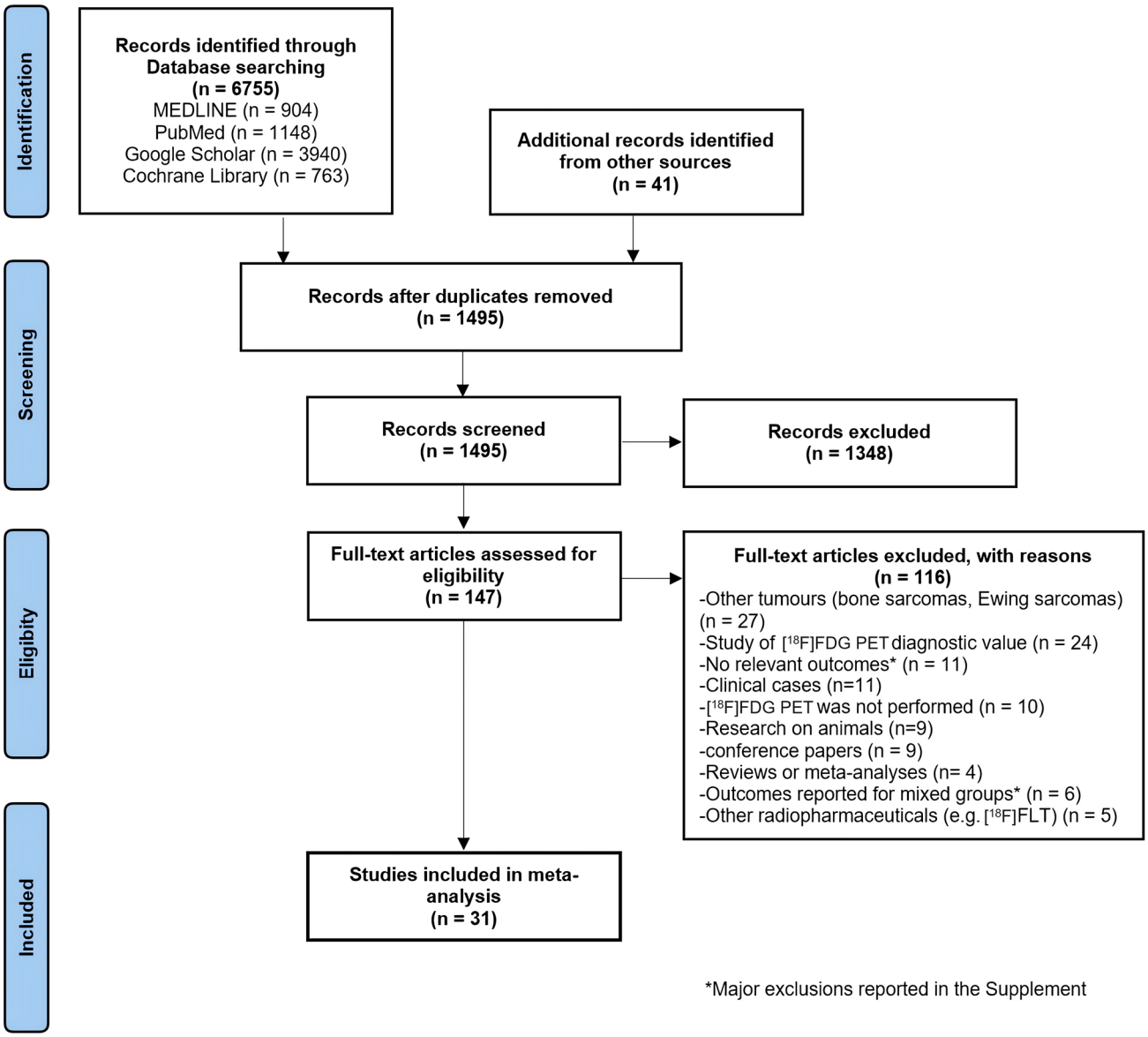

Fig. 1 PRISMA flow diagram for study selection

studies ($n = 964$, HR = 3.95, $p < 0.001$, $I^2 = 3$) and was non-significant in 'pediatric' studies ($n = 348$, HR = 1.14, $p = 0.4$, Fig. 3).

SUV2: A significant relationship was found between high SUV2 and poor EFS across three studies ($n = 163$, HR = 3.13, $p < 0.001$, high heterogeneity: $I^2 = 59\%$; Supplemental Fig. 3, Table 3), as was the SUV2 and OS relationship ($n = 163$, HR = 2.09, $p = 0.001$, $I^2 = 0\%$; Supplemental Fig. 3, Table 3). No subgroup analyses were conducted for these parameters.

SUV ratio: The analysis of five studies ($n = 432$) established a significant association between a low SUV ratio and improved EFS (HR = 0.61, $p = 0.049$, $I^2 = 22\%$; Supplemental Fig. 4, Table 3), particularly in 'adult' studies ($n = 77$, HR = 0.26, $p = 0.003$), but not in 'pediatric' ones ($n = 260$, HR = 0.87, $p = 0.6$, Table 3). Conversely, no significant association was found between SUV ratio and OS across five studies ($n = 283$, HR = 0.47, $p = 0.13$, high heterogeneity: $I^2 = 84\%$; Supplemental Fig. 4, Table 3).

MTV1: An assessment of five studies on MTV1 and EFS encompassing 317 patients revealed a significant association (HR = 2.29, $p = 0.011$, high heterogeneity: $I^2 = 75\%$; Supplemental Fig. 5, Table 3), which was stronger in 'adult' studies ($n = 153$, HR = 3.54, $p < 0.001$, $I^2 = 0$), but not significant in 'pediatric' studies ($n = 164$, HR = 1.54, $p = 0.4$, Table 3). The MTV1 and OS correlation across nine studies ($n = 381$) was also significant (HR = 3.05, $p < 0.001$, high heterogeneity: $I^2 = 72\%$; Supplemental Fig. 5, Table 3), and was significant

Table 1 Characteristics and description of eligible studies included in the meta-analysis

Study	Patient source	Study period	Follow up, months (Me)	Design	N of patients	Age, Me (range), y	Pediatric patients (≤21 y), %	Sex (M), %	End points	Cancer type	Stage of disease (metastatic), %	Histological grade, FNCLCC (high grade), %	Non-extermity location, %	HR estimation method	Journal
Andersen 1, 2015 [33]	Denmark	2002–2012	26.4	Retro, S	55	55.2 (18.7–86.3)	<25	47.3	OS	STS	27	100	18	Prov	Medicine
Andersen 2, 2015 [34]	Denmark	2002–2012	26.4	Retro, S	55	55.2 (18.7–86.3)	<25	47.3	OS	STS	27	100	18	Prov.; Indir. calc	Medicine
Andreou, 2014 [35]	Germany	2006–2012	40	Retro, S	35	58 (27–81)	≈ 0	51.4	EFS, OS	STS	0	91.4	0	Indir. calc	Eur J Nucl Med Mol Imaging
Annovazzi, 2022 [36]	Italy	2012–2020	50.7	Retro, S	51	62 (IQR 54–72)	≈ 0	60.8	EFS, OS	STS	0	100	13.7	Prov	J Clin Med
Casey, 2014 [13]	USA	2002–2013	63.6	Retro, S	86	10.9 (0.2–44)	≥75	50	EFS, OS	STS	41	NA	77	Indir. calc	Int J Radiation Oncol
Chang, 2014 [37]	Korea	2001–2011	73	Retro, S	20	35 (8–56)	<25	55	OS	STS	35	100	35	Prov.; Indir. calc	Nucl Med Mol Imaging
Chen, 2022 [38]	China	2014–2020	NR	Retro, S	19	59 (27–79)	≈ 0	47.4	OS	STS	57.9	89.5	NR	Prov	Quant Imaging Med Surg
Choi, 2013 [40]	Korea	2008–2011	23.7	Retro, S	66	52.1 (15–86)	<25	62	EFS	STS	14	84	0	Prov.; Indir. calc	Eur J Nucl Med Mol Imaging
Dharmarajan, 2012 [41]	USA	2001–2010	36	Retro, S	58	11 (0.2–43)	≥75	50	EFS	STS	34	NA	78	Indir. calc	Int J Radiation Oncol Biol Phys
El-Kholy, 2019 [12]	Egypt	2010–2016	NR	Retro, S	98	5.8 (0.3–17.5)	100	51	EFS, OS	STS	NR	NA	73.5	Indir. calc	Nucl Med Commun
Fayolle, 2022 [42]	France	2007–2017	40	Retro, M	101	7.4 (IQR 4–12.5)	100	61.4	EFS, OS	STS	22.8	NA	74.3	Prov.; Indir. calc	PLOS ONE
Fendler, 2015 [43]	Germany	2008–2013	22.2	Retro, M	73	52 (IQR 24)	<25	49	EFS	STS	25	99	63	Prov	J Nucl Med

Table 1 (continued)

Study	Patient source	Study period	Follow up, months (Me)	Design	N of patients	Age, Me (range), y	Pediatric patients (≤21 y), %	Sex (M), %	End points	Cancer type	Stage of disease (metastatic), %	Histological grade, FNCLCC (high grade), %	Non-extermity location, %	HR estimation method	Journal
Ha, 2016 [44]	Korea	2004–2014	60	Retro, S	36	50 (IQR 26–61)	<25	44	EFS, OS	STS	2.8	88.9	100	Prov	Eur J Nucl Med Mol Imaging
Hack, 2021 [15]	Switzerland	2001–2014	47	Retro, S	51	57 (IQR 36–73)	<25	58.8	OS	STS	19.6	39.2	NR	Indir. calc	Life
Harrison 1, 2021 [45]	USA	2006–2018	36	Pro, M	111	NR (53.8% < 10 y; others ≥ 10 y)	≥75	51.5	EFS	STS	0	NA	84.6	Prov	Cancer Med
Harrison 2, 2021 [45]	USA	2010–2018	36	Pro, M	95	NR (22% < 10 y; others ≥ 10 y)	50–75	50.5	EFS	STS	100	NR	71.4	Prov	Cancer Med
Hermann, 2012 [46]	USA	2005–2008	55	Pro, S	57	53 (20–86)	≈ 0	49	OS	STS	0	100	19	Prov	Clin Cancer Res
Hong, 2014 [47]	Korea	2003–2009	29	Retro, S	55	39 (21–55)	<25	62	OS	STS	27	95	56	Indir. calc	Skeletal Radiol
Jo, 2022 [48]	Korea	2001–2020	37.8	Retro, S	129	56.4 (SD 12.2)	≈ 0	48.1	EFS, OS	STS	13.2	77.5	100	Prov	Front Oncol
Kalisvaart, 2021 [49]	Netherlands	2017–2021	32	Retro, S	31	59 (SD 18)	≈ 0	65	OS	STS	100	93	32	Indir. calc	Diagnostics
Kato, 2020 [50]	Japan	2009–2018	16.9	Retro, M	16	68 (24–88)	≈ 0	75	OS	STS	31.3	62.5	100	Prov	Am J Roentgenol
Kitao, 2019 [51]	Japan	2010–2016	NR	Retro, S	20	59 (18–87)	<25	50	OS	STS	15	70	55	Indir. calc	Ann Nucl Med
Lisle, 2008 [52]	USA	1995–2007	63.4	Pro, M	44	35 (8–70)	<25	36	EFS, OS	STS	41	94	30	Prov	Clin Orthop Relat Res
Okazumi, 2009 [20]	Germany	NR	NR	Retro, S	26	NR	NR	NR	OS	STS	NR	71.9	41	Prov	Hell J Nucl Med

Table 1 (continued)

Study	Patient source	Study period	Follow up, months (Me)	Design	N of patients	Age, Me (range), y	Pediatric patients (≤21 y), %	Sex (M), %	End points	Cancer type	Stage of disease (metastatic), %	Histological grade, FNCLCC (high grade), %	Non-extermity location, %	HR estimation method	Journal
Parambil, 2023 [39]	India	2013–2018	38	Retro, S	63	5 (1–15)	100	68.3	EFS, OS	STS	12.7	NA	92.1	Prov	J Pediatr Hematol Oncol
Park, 2017 [14]	Korea	2007–2015	20	Retro, M	19	51 (38–76)	≈ 0	NR	EFS, OS	STS	47.3	NR	100	Indir. calc	J Gynecol Oncol
Rhu, 2019 [53]	Korea	2007–2018	60	Retro, S	133	55.9 (SD 11.8)	≈ 0	54.9	EFS, OS	STS	0.6	72.8	100	Prov	Sci Rep
Sambri, 2019 [54]	Italy	2004–2017	35	Retro, S	50	52 (19–79)	< 25	68	EFS, OS	STS	34	100	26	Indir. calc	Nucl Med Commun
Tateishi, 2011 [55]	Japan	NR	31	Pro, S	42	54 (32–72)	≈ 0	62	EFS, OS	STS	0	100	57	Prov.; Indir. calc	Clin Nucl Med
Umemura, 2017 [56]	Japan	2006–2016	18	Retro, S	18	74 (34–91)	≈ 0	66.7	OS	STS	0	NR	88.9	Prov	J Dermatol
Wakamatsu, 2021 [57]	India	2010–2021	41.8	Retro, S	201	64 (31–85)	≈ 0	50.2	OS	STS	6.5	61.7	NR	Prov	Cancers
Yamamoto, 2017 [58]	India	2005–2013	36	Retro, S	18	58.9 (NR)	≈ 0	NR	EFS, OS	STS	NR	NR	NR	Indir. calc	Oncotarget

HR hazard ratio, *NR* not reported, *NA* not applicable, *STS* soft-tissue sarcoma, *EFS* event-free survival, *OS* overall survival, *Retro* retrospective, *Pro* prospective, *S* single center, *M* multicenter, *SD* standard deviation, *IQR* interquartile range, Me median, *Prov* provided, *Indir. calc* indirectly calculated, *FNCLCC* Federation Nationale des Center de Lutte Contre le Cancer Sarcoma Group

Table 2 Methods of [^{18}F]FDG PET imaging of the included studies

Study	PET scanners	Fasting duration	Pre-injection blood glucose test, mg/dl	Post-injection interval, min	Dose of [^{18}F]FDG	[^{18}F]FDG PET time-Points	[^{18}F]FDG PET parameters	Segmentation method for MTV and TLG	Cut-off determination	SUV type	post-NAC criteria
Andersen 1, 2015 [33]	Biograph, GE; Discovery LS, GE	6	NR	60	400 MBq	Baseline	SUV1	NA	ROC	max	NA
Andersen 2, 2015 [34]	Biograph, GE; Discovery LS, GE	6	NR	60	400 MBq	Baseline	TLG1, MTV1	40%	ROC	NA	NA
Andreou, 2014 [35]	ECAT Exact 47, Siemens; Gemini, Philips	12	NR	120	300 MBq	Baseline, post-NAC	SUV2, SUV ratio	NA	ROC	max	After completion of NAC
Annovazzi, 2022 [36]	Biograph 16, Siemens	6	< 150	60	5 MBq/Kg	Baseline	MTV1, TLG1	SUV 2.5	NR	max	NA
Casey, 2014 [13]	NR	12	NR	90	370–550 MBq	Baseline, post-NAC	SUV1, SUV2, SUV ratio	NA	ROC	max	After completion of NAC
Chang, 2014 [37]	Biograph 6, Siemens	6	< 129.6	NR	7.4 MBq/Kg	Baseline	SUV1, TLG1, MTV1	SUV 2.5	ROC	max	NA
Chen, 2022 [38]	Biograph 16, Siemens	4 to 6	< 180	40 to 60	3.75–5.55 MBq/kg	Baseline	MTV1	SUV 2.5	ROC	max	NA
Choi, 2013 [40]	Gemini, Philips; Biograph 40, Siemens	6	NR	60	5.18 MBq/kg	Baseline	SUV1, TLG1, MTV1	40%	ROC	max	NA
Dharmarajan, 2012 [41]	NR	12	NR	90	370–550 MBq	Baseline, post-NAC	SUV1	NA	Median	max	NA
El-Kholy, 2019 [12]	Biograph, Siemens	4 to 6	< 150	45 to 60	4–5 MBq/Kg	Baseline	SUV1	NA	ROC	max	NA
Fayolle, 2022 [42]	Varied	5	< 120	60	NR	Baseline	SUV1, MTV1	40%	min p-value	max	NA
Fendler, 2015 [43]	Biograph 64, Siemens; Discovery 690, GE	6	93	90	254 MBq	Baseline, post-NAC	SUV1	NA	ROC	peak	NA
Ha, 2016 [44]	Biograph Sensation 16, Siemens; Discovery STE 8, GE	6	< 150	60	370–550 MBq	Baseline	SUV1, MTV1, TLG1	SUV 2.5	ROC	max	NA

Table 2 (continued)

Study	PET scanners	Fasting duration	Pre-injection blood glucose test, mg/dl	Post-injection interval, min	Dose of [^{18}F]FDG	[^{18}F]FDG PET time-Points	[^{18}F]FDG PET parameters	Segmentation method for MTV and TLG	Cut-off determination	SUV type	post-NAC criteria
Hack, 2021 [15]	GE Healthcare DSTX	6	< 120	45 to 60	2–4 MBq/Kg	Baseline	SUV1	NA	ROC	max	NA
Harrison 1, 2021 [45]	NR	NR	NR	62	3 MBq/Kg	Baseline, interim, post-NAC	SUV1, SUV ratio	NA	NR	max	After completion of NAC (week 15)
Harrison 2, 2021 [45]	NR	NR	NR	62	3 MBq/Kg	Baseline, interim, post-NAC	SUV1, SUV ratio	NA	NR	max	After completion of NAC (week 19)
Herrmann, 2012 [46]	Biograph Duo, Siemens	6	< 180	NR	7.77 MBq/Kg	Baseline, post-NAC	SUV ratio	NA	ROC	peak	After completion of NAC
Hong, 2014 [47]	Discovery LS, GE	6	< 160	45	5.5 MBq/Kg	Baseline	SUV1	NA	Cut-point analysis	max	NA
Jo, 2022 [48]	Discovery STE, GE	6	< 200	60	5 MBq/Kg	Baseline	SUV1	NA	ROC	max	NA
Kalisvaart, 2021 [49]	Philips Healthcare, Best	6	NR	60	NR	Baseline	SUV1	NA	Median	max	NA
Kato, 2020 [50]	Varied	4	NR	58	2–5 MBq/kg	Baseline	SUV1, MTV1, TLG1	SUV 2.5	min p-value	max	NA
Kitao, 2019 [51]	Eminence SET-3000G	6	< 150	62	2.9–4.6 MBq/Kg	Baseline	SUV1, MTV1, TLG1	SUV 2.0	Median	max	NA
Lisle, 2008 [52]	Advance Positron Tomograph, GE	12	NR	45	370 MBq	Baseline	SUV1	NA	Median	max	NA
Okazumi, 2009 [20]	ECAT, Siemens	NR	NR	60	300–370 MBq	Baseline	SUV1	NA	NR	mean	NA
Parambil, 2023 [39]	NR	NR	NR	NR	NR	Baseline, post-NAC	SUV1, SUV ratio, MTV1, TLG1	NR	Cut-point analysis	max	After completion of NAC
Park, 2017 [14]	NR	4	NR	60	5.2 MBq/kg or 370 MBq	Baseline	SUV1	NA	ROC	max	NA
Rhu, 2019 [53]	Discovery STE, GE	6	< 200	60	5.0 MBq/kg	Baseline	SUV1	NA	ROC	max	NA

Table 2 (continued)

Study	PET scanners	Fasting duration	Pre-injection blood glucose test, mg/dl	Post-injection interval, min	Dose of [^{18}F] FDG	[^{18}F]FDG PET time-Points	[^{18}F]FDG PET parameters	Segmentation method for MTV and TLG	Cut-off determination	SUV type	post-NAC criteria
Sambri, 2019 [54]	Discovery LS, GE	6	NR	60	3.7 MBq/Kg	Baseline	SUV1	NA	Previous report (ROC)	max	NA
Tateishi, 2011 [55]	Aquiduo, Toshiba	6	NR	60	380–401 MBq	Baseline, interim, post-NAC	SUV1, SUV2, SUV ratio	NA	Median	max	After completion of NAC
Umemura, 2017 [56]	NR	NR	NR	NR	NR	Baseline	SUV1	NA	Median	max	NA
Wakamatsu, 2021 [57]	NR	NR	NR	NR	NR	Baseline	SUV1	NA	Median	max	NA
Yamamoto, 2017 [58]	NR	4	NR	50	NR	Baseline	SUV1	NA	ROC	max	NA

PET positron emission tomography, *FDG* Fluorodeoxyglucose, *NAC* neoadjuvant chemotherapy, *SUV* standardized uptake value, *TLG* total lesion glycolysis, *MTV* metabolic tumor volume, *ROC* curve receiver operating characteristic curve, *NR* not reported, *NA* not applicable

in 'adult' studies ($n = 217$, HR = 4.06, $p < 0.001$) and non-significant in 'pediatric' studies ($n = 164$, HR = 1.51, $p = 0.4$, Table 3).

TLG1: Exploration of TLG1 and EFS in four studies with 216 patients demonstrated a significant association (HR = 2.85, $p = 0.032$, high heterogeneity: $I^2 = 77\%$; Supplemental Fig. 6, Table 3). The TLG1 and OS relationship across seven studies ($n = 261$) also revealed a significant association (HR = 3.23, $p = 0.002$, high heterogeneity: $I^2 = 67\%$; Supplemental Fig. 6, Table 3). Subgroup analyses were not performed for these correlations.

Risk of bias and GRADE assessment

The overall risk of bias of the 31 enrolled studies was judged as 'low' in three trials, 'some concerns' in 9 trials and 'high' in 16 trials (Supplemental Fig. 1). The primary sources of bias were the lack of matching for confounding variables, inconsistent follow-up, and variation in co-interventions among the studies.

Egger's test and funnel plot analysis revealed presence of publication bias and small-study effects for the majority of the analyses (Table 3, Supplemental Figs. 7–11).

Moderate level of evidence (GRADE approach) was stated for the evidence of decreased EFS and OS in adult patients with high SUV1 and MTV1 (Supplemental Table 4). However, the certainty of evidence for other [^{18}F] FDG PET metabolic parameters was classified as 'very low'.

Meta-regression

The meta-regression analysis revealed patient age as the only significant modifier of the association between SUV1 and survival outcomes (Supplemental Table 5). Specifically, an elevation in the average patient age within the study was significantly tied to an amplified HR for SUV1 and survival outcomes (Coeff. 0.016 for EFS and 0.026 for OS, $p < 0.001$, Fig. 3, Supplemental Figs. 13, 14). An inverse correlation was observed between the average patient age in the studies and the proportion of patients diagnosed with high-grade tumors (Supplemental Table 6 and Supplemental Fig. 12).

Trial sequential analysis

For association between SUV1 and survival outcomes in adult patients with STS the TSA analysis showed that the cumulative *z*-curve, after crossing the O'Brien–Fleming boundary for effect, did not reach the required sample size (2007 patients for EFS and 3191 patients for OS, Supplemental Figs. 15 and 17). These TSAs suggest that, although the pooled effect is statistically significant, with regard to sample size, the result is not definitive to reach 90% study power, and future studies are necessary to be conclusive.

Table 3 Relationship between [^{18}F]FDG PET parameters and survival outcomes and of sensitivity analysis results

Outcome		Studies, *N*	Cohorts, *N*	Patients, *N*	HR	95% CI	*p* value for overall effect	*p* value for heterogeneity	I^2, %	*p* value for publication bias (Egger's test)	Effect model
Event-free survival											
SUV1	Univariate analysis	16	17	1222	1.68	1.31–2.14	< 0.001	< 0.001	94	< 0.001	Random
	Multivariable analysis	5	5	443	1.75	1.07–2.86	0.025	< 0.001	81	< 0.001	Random
	Pediatric patients	6	6	517	1.14	0.93–1.39	0.2	0.07	76	0.005	Random
	Adults	10	10	610	2.49	1.96–3.17	< 0.001	0.8	0	0.3	Fixed
	Low-moderate bias studies	7	7	548	1.82	1.21–2.73	0.004	< 0.001	77	0.04	Random
SUV2	Univariate analysis	3	3	163	3.13	1.61–6.1	< 0.001	0.1	59	0.034	Random
SUV ratio	Univariate analysis	5	6	432	0.61	0.38–0.99	0.049	0.2	22	0.075	Fixed
	Pediatric patients	3	3	260	0.87	0.53–1.43	0.6	0.9	0	0.6	Fixed
	Adults	2	2	77	0.26	0.11–0.63	0.003	0.3	8.7	NA	Random
MTV1	Univariate analysis	5	5	317	2.29	1.21–4.33	0.011	< 0.001	75	< 0.001	Random
	Multivariable analysis	2	2	137	3.08	1.6–5.95	< 0.001	0.4	0	NA	Random
	Pediatric patients	2	2	164	1.54	0.59–4.05	0.4	0.007	86	NA	Random
	Adults	3	3	153	3.54	1.89–6.65	< 0.001	0.9	0	0.7	Fixed
	Low-moderate bias studies	3	3	200	1.94	0.78–4.8	0.15	0.003	81	< 0.001	Random
TLG1	Univariate analysis	4	4	216	2.85	1.1–7.4	0.032	< 0.001	77	< 0.001	Random
	Multivariable analysis	2	2	102	5.36	2.24–12.85	< 0.001	0.8	0	NA	Random
Overall survival											
SUV1	Univariate analysis	22	22	1312	3.07	2.2–4.28	< 0.001	< 0.001	74	0.001	Random
	Multivariable analysis	8	8	725	2.84	1.47–5.51	0.002	< 0.001	82	< 0.001	Random
	Pediatric patients	4	4	348	1.14	0.86–1.51	0.4	0.15	44	0.3	Fixed
	Adults	18	18	964	3.95	3.1–5.03	< 0.001	0.7	1.3	0.06	Fixed
	Low-moderate bias studies	11	11	890	2.94	1.79–4.83	< 0.001	< 0.001	84	< 0.001	Random
SUV2	Univariate analysis	3	3	163	2.09	1.34–3.26	0.001	0.3	0	0.16	Fixed
SUV ratio	Univariate analysis	5	5	283	0.47	0.17–1.26	0.13	0.004	84	0.5	Random
	Multivariable analysis	2	2	99	0.16	0.03–0.8	0.025	0.05	73	NA	Random
	Pediatric patients	2	2	149	1	0.5–2	0.9	0.5	0	NA	Random
	Adults	3	3	134	0.27	0.07–1.11	0.065	0.021	74	0.4	Random
	Low-moderate bias studies	3	3	162	0.28	0.27–1.1	0.067	0.012	77	0.066	Random
MTV1	Univariate analysis	9	9	381	3.05	1.78–5.22	< 0.001	< 0.001	72	< 0.001	Random
	Multivariable analysis	3	3	156	3.89	2.01–7.54	< 0.001	0.3	23	0.4	Fixed
	Pediatric patients	2	2	164	1.51	0.59–3.88	0.4	0.009	85	NA	Random
	Adults	7	7	217	4.06	2.61–6.31	< 0.001	0.8	0	0.2	Fixed
	Studies with low-moderate risk of bias	4	4	255	1.97	1.03–3.78	0.04	0.001	77	< 0.001	Random

Table 3 (continued)

Outcome		Studies, *N*	Cohorts, *N*	Patients, *N*	HR	95% CI	*p* value for overall effect	*p* value for heterogeneity	I^2, %	*p* value for publication bias (Egger's test)	Effect model
TLG1	Univariate analysis	7	7	261	3.23	1.57–6.67	0.002	0.001	67	< 0.001	Random
	Multivariable analysis	2	2	91	4.48	1.86–10.79	< 0.001	0.5	0	NA	Random
	Low-moderate bias studies	3	3	154	2.04	0.78–5.36	0.15	0.007	76	0.012	Random

HR hazard ratio, *SUV* standardized uptake value, *TLG* total lesion glycolysis, *MTV* metabolic tumor volume, *CI* confidence interval, *NA* not applicable

Conversely, when exploring the association between SUV1 and survival outcomes in pediatric patients, the cumulative *z*-curve lies in the zone with no statistical significance and not reach the required sample size (1475 patients for EFS and 1695 patients for OS, Supplemental Figs. 16 and 18). This implies that the sample size of the meta-analysis was too small, and it is therefore impossible to infer where the cumulative z-line will lie in future trials.

Discussion

Key findings

Our principal finding suggests that high SUV1 (moderate evidence), SUV2 (very low evidence), MTV1 (moderate evidence) and TLG1 (very low evidence) values are strongly associated with unfavorable EFS and OS in adult patients with STS (all HRs ≥ 2). According to the proposed prognostic factor categories of Hayes et al., a HR exceeding 2 might be regarded as a strong prognostic factor [59]. However, very low-level evidence suggests that no [^{18}F]FDG PET metabolic parameter is associated with survival outcomes in pediatric patients with RMS. The SUV ratio parameter demonstrated contradictory results—it was associated with EFS in adult patients, yet showed no correlation with OS.

The meta-regression analysis revealed that patient age is a significant modifier of the association between SUV1 and survival outcomes, thus emphasizing the role of patient age in the predictive value of [^{18}F]FDG PET metabolic parameters.

The TSA analysis indicated that further research is necessary for definitive conclusions, especially in the pediatric patient population.

Relationship with previous studies

The results of our systematic review and meta-analysis are largely consistent with previous meta-analyses highlighting the prognostic potential of various [^{18}F]FDG PET metabolic parameters in oncological settings. Specifically, meta-analyses have indicated the utility of SUV, MTV, and TLG parameters in predicting survival outcomes in patients with STS [17–19].

In particular, our findings corroborate previous research suggesting that higher pre- and posttreatment SUV values can predict poor survival outcomes. This is consistent with prior studies indicating that higher SUV values, reflecting high metabolic activity of the tumor and the proliferation rate of tumor cells, are associated with aggressive tumor behavior and poorer patient outcomes [60, 61]. In the systematic review by Lim et al. (2019), it was also demonstrated that a reduction in SUVmax correlates with improved

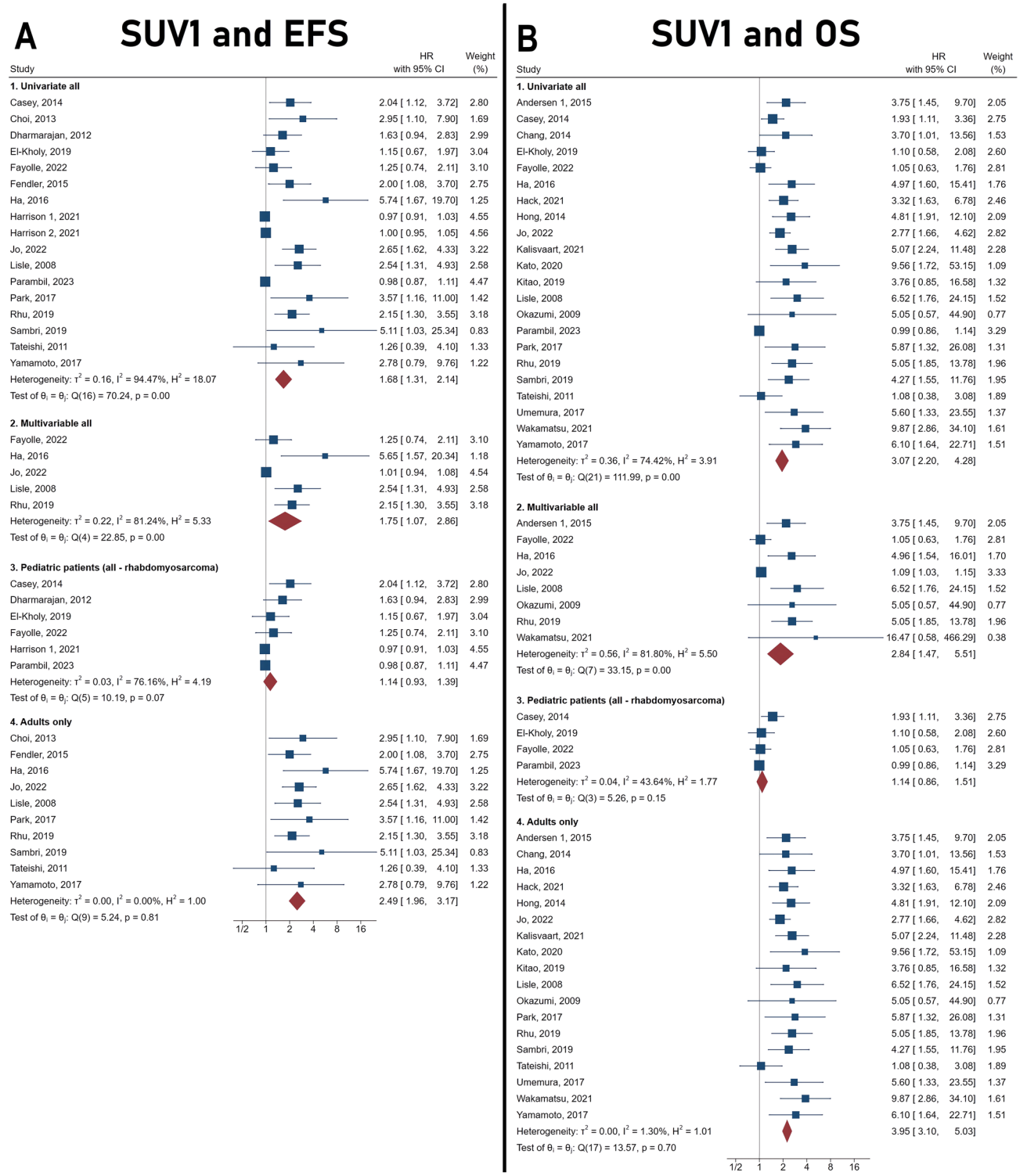

Fig. 2 Forest plot for event-free survival (**A**) and overall survival (**B**) representing the Hazard ratios (HRs) for high pretreatment SUV values versus low values. The plot displays the study, HR with confidence interval (CI), heterogeneity parameters and *p* value. The size of the squares indicates the weight of the studies, the diamond represents the pooled HR with CI

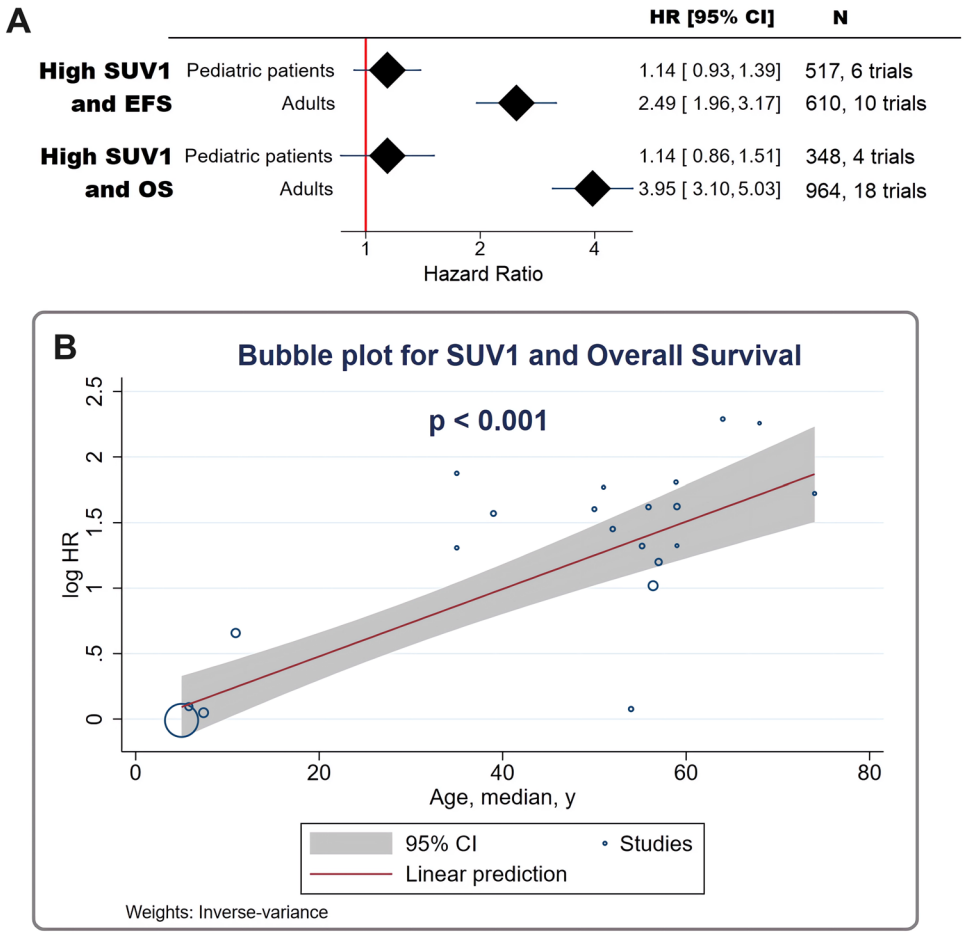

Fig. 3 Forest plot **A** for event-free survival (EFS) and overall survival (OS) in pediatric patients and adults with high SUV1 versus low SUV1 and bubble plot **B** depicting the univariate meta regression of log HR with median patient's age (for association between SUV1 and OS)

recurrence-free survival in patients with STS. Furthermore, they found a strong correlation between SUV and tumor grade, with the majority of intermediate/high-grade STS exhibiting significantly higher SUVmax values [16]. Similar to the study by Li et al., we found no significant relationship between SUV ratio and OS [17]. While the SUV ratio demonstrated a significant correlation with EFS, especially in adult patients, the lack of a significant association with OS might be attributed to high clinical and statistical heterogeneity of included studies.

Similarly, our results align with previous research demonstrating that higher MTV and TLG values are associated with poorer survival outcomes. MTV refers to the volume of the lesion that exhibits metabolic activity, while TLG represents the product of the average SUV of the lesion and the MTV. These parameters provide volumetric and functional information about tumor metabolic activity and can theoretically more accurately reflect the actual tumor burden [62], and their association with survival outcomes has been reported in numerous cancers, including sarcomas [17–19, 63–65]. It's notable that the MTV and TLG data used in this meta-analysis was obtained from pre-chemotherapy [^{18}F]FDG PET imaging. Currently, there is no evidence regarding the prognostic value of MTV and TLG derived from post-chemotherapy imaging in patients with STS.

However, we observed that all associations of [^{18}F]FDG PET metabolic parameters with survival outcomes were generally stronger in adult studies compared to pediatric ones, which is an aspect not examined in previous studies.

Significance of study findings

Our findings suggest that high SUV1, SUV2, and pretreatment MTV and TLG values can serve as predictors of EFS and OS, highlighting their potential as prognostic markers in patients with STS. Thus, it might be beneficial for physicians to adopt a more stringent follow-up regimen with reduced intervals for patients exhibiting high SUV1, MTV1 or TLG1 values. Furthermore, low SUV2 values may also suggest well chemotherapy response.

In our study, pretreatment MTV and TLG parameters showed higher HR values than SUV. The predictive advantage of MTV and TLG over SUV may stem from their ability to better reflect the tumor's overall metabolic burden, which is associated with tumor aggressiveness and patient prognosis. These parameters consider the metabolic heterogeneity

within the entire tumor, rather than a single point, which can often lead to a more accurate prediction of treatment outcomes.

It should be noted that the strength of associations between PET metabolic parameters and survival outcomes varied between adult and pediatric populations. Moreover, the meta-regression analysis revealed patient age as a significant modifier of the association between SUV1 and survival outcomes, underscoring the importance of considering age-specific factors in prognostic assessments. The prognosis impact of [^{18}F]FDG uptake might be different in adult or pediatric patients as none of the previous meta-analyses were realized in a strictly pediatric population [66]. In the literature, the prognostic relevance of patient age remains controversial, older age seems to be associated with a worse outcome in both STS [67], osteosarcoma [68] and Ewing's sarcoma [69]. Additionally, our research indicated that younger patients tend to have tumors of a higher histological grade. This observation leads us to speculate that the contrasting impacts of SUVs on prognostic outcomes between pediatric and adult populations, as documented in our study, could be attributed to these underlying variations in tumor biology. These biological differences could lead to variable responses to systemic cytotoxic therapy across age groups.

It is crucial to emphasize that our conclusions regarding the lack of impact of [^{18}F]FDG PET parameters on prognosis in the pediatric population were based solely on patients with rhabdomyosarcoma. Unlike "adult-type" sarcomas, rhabdomyosarcoma is characterized by high sensitivity to chemotherapy. Moreover, pediatric patients typically undergo more aggressive treatment protocols compared to adults due to their better overall health and ability to tolerate intensive therapies, which can affect the metabolic activity of the tumor and potentially the utility of [^{18}F]FDG PET parameters.

This systematic review and meta-analysis also provide an overview of the heterogeneity present in current studies with regards to methodological aspects, such as [^{18}F]FDG PET scanning protocols and cut-off value determination methods. These findings underscore the need for standardized protocols and analytical methods to further enhance the reliability and reproducibility of research in this field.

Strengths and limitations

To our knowledge, this is the largest meta-analysis designed to systematically explore the relationships between [^{18}F]FDG PET parameters and survival outcomes in patients with STS. Unlike some previous studies, we avoided combining different sarcoma types. Bone sarcomas, STS and Ewing's sarcomas are heterogeneous groups, each possessing unique histological subtypes, molecular profiles, and clinical behaviors that can influence [^{18}F]FDG uptake patterns. For instance, some soft-tissue sarcomas (STS) may exhibit higher metabolic rates, leading to increased [^{18}F]FDG uptake, compared to certain bone sarcomas [15, 70, 71]. Combining these groups can consequently mask the distinct correlations between [^{18}F]FDG PET parameters and survival outcomes. In studies that included patients with various types of sarcomas, including bone sarcomas and Ewing's sarcoma, we exclusively extracted data pertaining to patients STS.

Notably, our study is the first to investigate and highlight the differences in the prognostic value of [^{18}F]FDG PET metabolic parameters between adult and pediatric patients with STS. We found a significant impact of age on the association between SUV1 and survival outcomes.

We performed an extensive subgroup analysis including multivariable data analysis based on Cox proportional hazards model, that reduces bias from some major confounding variables. Furthermore, we executed an additional analysis in studies with low-moderate risk of bias, complemented by meta-regression and trial sequential analysis.

In addition, some limitations of this review must be acknowledged. One of the main limitations is the high level of heterogeneity observed among the included studies. This heterogeneity could stem from factors such as variations in study design, scanning protocols, methods for determining cut-off values, and patient demographics, which could affect the findings and their interpretation. On the other hand, the robustness of the results, despite the heterogeneity of the studies, may indicate high transitivity of the results and high quality of evidence. The included studies employed various segmentation methods to derive MTV for survival prediction, potentially leading to diverse MTV estimations, and consequently, impacting the TLG values [72].

Second, considering that 14 out of the 31 studies included in our meta-analysis represented mixed cohorts of pediatric and adult patients, we opted for a cut-off point of 75% children to categorize a study as 'pediatric'. This could, however, have introduced a potential skewness in our results.

Third, although our meta-analysis exclusively focused on STS, it incorporates diverse STS types, including RMS, synovial sarcoma, angiosarcoma, liposarcoma, leiomyosarcoma, etc. This could also have affected the results, as different STS variants depending on histologic type and histological grade may exhibit varying levels of [^{18}F]FDG accumulation [70, 73]. Significant variability precluded a subgroup analysis for different STS subtypes; however, it should be noted that all studies classified as 'pediatric' were solely represented by patients with RMS.

Fourth, the presence of publication bias and small-study effects for some analyses, as revealed by Egger's test and funnel plot analysis, suggest that those results should be interpreted with caution.

Fifth, another potential source of bias in our study may stem from our methods of HR extraction. In cases where HRs were explicitly provided, we incorporated them directly. However, when HRs were not stated, we derived them either from the outcome data given in the articles or extrapolated from survival curves using univariate analysis. Therefore, this may have potentially introduced bias into meta-analysis.

Lastly, the overall risk of bias in the included studies was either 'high' or of 'some concerns' for the majority of the trials. Most common sources of bias were the lack of matching for confounding variables, inconsistent follow-up, and variation in co-interventions among the studies. These factors may have affected the reported associations and thus, the interpretations drawn from our meta-analysis.

Future studies and prospects

Looking ahead, future research can address the limitations observed in meta-analysis. Investigating the prognostic significance of post-chemotherapy MTV and TLG, as well as examining the changes in these parameters from pre- to post-chemotherapy in the context of predicting chemotherapy response, could provide intriguing prospects for future studies. To assess the impact of baseline and post-therapy PET/CT parameters on survival rates, additional prospective clinical studies with clearly defined time points are needed for evaluating PET/CT parameters in patients with various biological types of rhabdomyosarcoma (fusion-positive and fusion-negative). Special interest may be in organizing and conducting similar studies in children and adolescents with "adult-type" soft-tissue sarcomas, which, in terms of their biology and sensitivity to chemotherapy, are much closer to similar tumors in adults compared to rhabdomyosarcoma. Results of TSA analysis suggests that there is a need for prospective, multicenter studies with a more uniform methodological design. The protocols for [^{18}F]FDG PET scanning, segmentation methods and the methods to determine cut-off values should be standardized across these studies to ensure consistency and comparability of results. This can contribute to a more robust and generalizable evidence base regarding the prognostic value of PET parameters in patients with STS.

Conclusion

In conclusion, our systematic review and meta-analysis provide evidence that [^{18}F]FDG PET parameters of SUV1, SUV2, MTV1, and TLG1, hold significant prognostic value for event-free survival and overall survival in adult patients with STS. Notably, we found that the association of these parameters with survival outcomes was non-significant in pediatric patients, underscoring the necessity of age-specific considerations in future research focused on investigating [18F]FDG PET prognostic parameters and their clinical application for patients with STS. Future well-designed prospective multicenter studies with uniform methodology are needed to validate our findings and further explore the value of clinical use of [^{18}F]FDG PET imaging in improving outcomes of patients with STS.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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