Systematic Review and Meta-Analysis

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Prognostic value of maximum standard uptake value, metabolic tumor volume, and total lesion glycolysis of ^{18}F-FDG PET/CT in patients with renal carcinoma

A protocol for systematic review and meta analysis

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Abstract

Purpose: We present a comprehensive systematic review of the documented literature on parameters derived from ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and meta-analysis of the prognostic value of maximal standard uptake value (SUVmax), metabolic tumor volume (MTV) and total lesional glycolysis (TLG) in patients with renal carcinoma (RCC).

Patients and methods: Relevant articles in English from PubMed, EMBASE, and the Cochrane Library were retrieved. Pooled hazard ratio (HR) values were used to assess the prognostic value of SUVmax, MTV, and TLG.

Results: A total of 10 primary studies involving 780 patients with RCC were included. The combined HRs for event-free survival were 1.32 (95% CI 1.10–1.58) for SUVmax, 2.40 (95% CI 1.20–4.79) for MTV, and 3.31 (95% CI 1.68–6.50) for TLG. Pooled HRs for overall survival were 1.264 (95% CI 1.124–1.421) for SUVmax, 3.52 (95% CI 1.451–8.536) for MTV, and 6.33 (95% CI 1.32–30.30) for TLG. Subgroup analysis revealed SUVmax as an independent risk factor for patients with recurrence or metastasis.

Conclusion: The present meta-analysis confirmed that despite the clinical heterogeneity of RCC and adoption of various methods between studies, high SUVmax is a significant prognostic factor, especially in patients with recurrence or metastasis. MTV and TLG were associated with prediction of higher risk of adverse events or death in patients with RCC.

Abbreviations: EFS= event-free survival, HR = hazard ratio, MTV = metabolic tumor volume, OS = overall survival, RCC = renal carcinoma, SUVmax = maximal standard uptake value, TLG = total lesional glycolysis.

Keywords: maximal standard uptake value, meta-analysis, metabolic tumor volume, positron emission tomography/computed tomography, renal carcinoma, total lesional glycolysis

1. Introduction

Renal cell carcinoma (RCC), the third most common urological malignancy worldwide, accounts for ~3% of all reported cancers[1] and continues to show a steady increase in incidence.[2] The cytokine treatments currently available for advanced RCC patients are associated with uncertain prognosis.[3,4] Prognosis in RCC patients can vary, and the guidelines recommend prognostic classification of treatments based on a combination of clinical and laboratory data.[5] Novel molecular targets, such as vascular endothelial growth factor (VEGF) or mTOR kinase, have been selected as treatment strategies to improve the therapeutic index.[6–9] For metastatic RCC, the most widely used prognostic models are the Memorial Sloan-Kettering Cancer Center model involving patients treated with interferon α,[10] Cleveland Clinic Foundation model,[11] International Kidney Cancer Working Group model,[12] and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.[13] However, these models are not completely satisfactory for evaluating individual patient treatment options and prognosis in the era of targeted therapies.

Accumulating evidence supports the prognostic significance of 18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET/CT) in prediction of malignant tumors, TNM staging, and evaluation of therapeutic effects. In particular, the FDG parameters of tumor metabolism and volume, maximal standard

Editor: Hongming Zhuang.

This research was supported by the National Natural Science Foundation of China (31760330) and (31860321).

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Xuan D, Wen W, Tian S, Piao M, Xu D, Liu L. Prognostic value of maximum standard uptake value, metabolic tumor volume, and total lesion glycolysis of ^{18}F-FDG PET/CT in patients with renal carcinoma: a protocol for systematic review and meta analysis. Medicine 2020;99:20(e19988).

Received: 6 February 2020 / Received in final form: 18 March 2020 / Accepted: 23 March 2020

http://dx.doi.org/10.1097/MD.0000000000019988

uptake value (SUVmax), metabolic tumor volume (MTV), and total lesional glycolysis (TLG), have received considerable research attention. MTV represents the size of tumor tissue that actively ingests ^{18}F- FDG and TLG is the median SUV value in the region of interest of MTV.[14–17] However, the effectiveness of ^{18}F-FDG PET/CT parameters in predicting survival rate in RCC patients remains a controversial issue. FDG PET is currently not a standard technique in the diagnosis and staging of RCC due to renal excretion. Studies investigating the efficacy of FDG PET in localized RCC have generated disappointing results to date.[18]

A significant relationship between high SUVmax and poor prognosis in patients with RCC has been reported by a number of studies[19,20] whereas no such correlation was observed by Hwang et al.[21] To clarify this association, a meta-analysis was designed to evaluate the prognostic value of SUVmax, MTV, and TLG in RCC patients.

2. Materials and methods

This systematic review and meta-analysis was conducted by following the guidelines of preferred reporting items of the systematic review and meta-analysis (PRISMA) statement.[22] All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

2.1. Inclusion criteria and literature source retrieval strategy

A systematic search of PubMed, Embase, and Cochrane Library (2010–2018) using the following keywords ("renal" OR "kidney") AND ("carcinoma" OR "tumor" OR "cancer" OR "neoplasm") AND ("positron emission tomography" OR "positron emission tomography-computed tomography" OR "positron emission tomography computed tomography" OR "PET"OR "PET-CT" OR "PET CT" OR "PET/CT" OR "fluorodeoxyglucose" OR "FDG") AND ("prognostic" OR "prognosis" OR "predictive" OR "survival" OR "outcome") was performed. Inclusion criteria were as follows:

(1) studies included histologically diagnosed RCC patients,
(2) ^{18}F-FDG PET/CT was used as an imaging tool before treatment,
(3) the study reported at least 1 form of survival data, and
(4) articles were published in English.

Exclusion criteria were as follows:

(1) studies focusing only on diagnosis, staging or monitoring recurrence or progression,
(2) studies involving patients with recurrent disease,
(3) reviews, case reports, conference abstracts, and editorial materials.

Based on the above criteria, 2 authors independently conducted screening of the literature and discrepancies were resolved by reaching a consensus. If the results reported were from the same sample, completed studies with the latest information were used.

2.2. Data extraction

Two authors (W Wen and D Xu) independently extracted the following data (Table 1):

(1) basic information, including the year of publication, first author, study time, follow-up duration, and study design,
(2) details of patients and tumors, including median age, sample size, histology, TNM staging, treatment measures, and endpoints.

^{18}F-FDG- PET scan data and parameters, fasting time before injection, blood glucose detection before injection, truncated interval value of the FDG injection dose, truncated values of the PET parameters SUVmax, MTV, TLG, and tumor profiles were additionally extracted (presented in Table 2).

2.3. Statistical analysis

We followed the same methodology used previously by our group.[23] Event-free survival (EFS) is defined as the time from treatment initiation to recurrence or progression. In this meta-analysis, disease-free survival, progression-free survival, and disease-free metastasis survival in the included studies were combined and redefined as EFS. Overall survival (OS) was defined as time from therapy initiation until death regardless of the cause.[24,25] As the effect size of each study, hazard ratio (HR) and 95% confidence interval (CI) take into account the number and time of events, and are considered more accurate and reliable than odds ratio (OR) and relative risk (RR). Combined HR and 95% CI values were calculated and effects of ^{18}F-FDG PET parameters, SUVmax, MTV, and TLG, on survival outcomes measured through effect size of HR to assess their potential correlation with prognosis of RCC patients. HR is the sum of differences between Kaplan–Meier survival curves and 2 groups during a specific follow-up period. Data on multivariate HR and 95% CI were directly extracted from studies. In cases where multivariate HR was not available, univariate HR was obtained. If both multivariate and univariate HRs were unavailable, the methodology recommended by Parmar et al[26] was used to reconstruct HR estimates and variance based on survival data from Kaplan–Meier survival curves read by Engauge Digitizer (version 9.4). HR $>$ 1 implied poorer survival whereas HR $<$1 implied a survival benefit in patients with high SUVmax, MTV, or TLG.

Statistical heterogeneity was measured using chi-squared Q test and I^2 statistic. Heterogeneity was considered to be present at $P < .05$ or/and $I^2 > 50\%$. A fixed- effects model was employed for meta-analysis when heterogeneity was not significant and a random-effects model applied in case of significant heterogeneity. To explore the sources of heterogeneity across studies, we did stratify and logistic meta-regression analyses. RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA version 12.0 (STATA Corp, College Station, TX) were applied for statistical analysis. Begg and Egger tests were used for evaluating bias using STATA version 12.0. P values $<.05$ were considered statistically significant.

3. Results

3.1. Search results

The literature search process is presented in Figure 1. Three databases were examined, which initially yielded 407 Embase articles, 150 PubMed articles and 15 Cochrane Library articles (572 articles in total). Upon excluding duplications and meeting summaries, 29 articles that did not meet the inclusion criteria were removed, 2 studies did not describe kidney cancer, 1 study introduced a case report, and there was no reliable data in 26 studies. Finally, 10 studies published from 2010 to 2018 including 780 patients that met the conditions of the study were

Table 1

Characteristics of the included studies.

Study	Year	Country	Study period	Follow-up duration (months)	Median age (range), years	No. of patients	TNM staging	End points	study design	Histology	Treatment
Famebo et al (2014)	2014	Sweden	2006–2010	1629 days (range 1280–2683)	65	39	metastatic	OS PFS	P	(Clear cell/papillary	Sorafenib/sunitinib/pazopanib Nephrectomy
Hwang et al (2017)	2017	Korea	2007–2013	20.2 (1.5–78.3)	60 (37–88)	56	Metastatic	OS PFS	R	NA	sorafenib/sunitinib/pazopanib
Ito et al (2017)	2017	Japan	2010–2015	11.7 (1.0–63.0)	63.5 (46–78)	30	metastatic	OS PFS	R	Clear cell Clear cell/sarcomatoid Papillary 1 Collecting duct	Sorafenib/sunitinib/pazopanib Cytokine therapy Nephrectomy
Nakaigawa et al (2016)	2016	Japan	2008–2014	18 (1–70)	65 (32–82)	101	stage IV or recurrent RCC	RFS	P	Clear cell Papillary Clear cell/Sarcomatoid Sarcomatoid Hemodialyssis Unclassified	IFN-α 9 IFN-α/sorafenib 2 Sorafenib 2 Sunitinib 1 S-1 1 IFN-α/UFT 1 Sorafenib
Nakaigawa et al (2017)	2017	Japan	2009–2016	15.4 (0.9–97.4)	66 (45–83)	81	advanced RCC	RFS	P	Clear cell Papillary Clear cell/sarcomatoid Clear cell/sarcomatoid Hemodialysis Others nephrectomy	Sorafenib Sunitinib Temsirolimus Axitinib Pazopanib Everolimus
Nakajima et al (2017)	2017	Japan	2013–2015	535 (13–895)d	62 (33–92)	139	I-IV	EFS OS	R	Clear cell carcinoma Papillary RCC Chromophobe RCC	Chemotherapy Radiotherapy
Namura et al (2010)	2010	Japan	2008–2009	262d (43–531)	61 (32–82)	26	recurrent diseases and stage IV	PFS	R	clear cell carcinoma papillary clear/sarcomatoid	Surgeries Nephrectomy metastatectomy
Yoon et al (2013)	2013	Korea	2006–2012	21.9 (2.9–78.7)	62 (28–89)	44	initial staging and recurred disease	OS	R	Clear cell Papillary Others	Sunitinib Sorafenib Everolimus Temsirolimus Pazopanib
Pankowska et al (2018)	2018	Japan	2011–2016	19 (3–61)	64 (41–83)	121	Recurrent Metastatic Regional Stage IV Metastatic Locoregional	DFS	R	Clear cell Papillary Hemodialysis Unclassified	IFN-α IFN-α/sorafenib Sorafenib Sunitinib
Kayani et al (2011)	2011	United Kingdom	2007–2010		61 (44–78)	43	I-IV	OS	P	Clear cell	Sunitinib

DFS = disease-free survival, EFS = event-free survival, NA = not available, OS = overall survival, P = prospective, PFS = progression-free survival, R = retrospective, RFS = recurrence/relapse free survival.

Table 2

Methods of ^{18}F-FDG PET imaging of included studies.

Study	Duration of fasting	Preinjection blood glucose -test	Postinjection interval	Dose of 18F-FDG	Pet parameters	Determination of cut-off values	Cut-off values		
							SUV	MTV (cm^3)	TLG
Farnebo et al (2014)	6 h	NA	1 h	4 MBq /kg	SUVmax	Others	2.3		
Hwang et al (2017)	6 h	140 mg/dL	1 h	5.5 MBq/kg	SUVmax MTV TLG	ROC curve	2.2	27.2	143.5 g
Ito et al (2017)	6 h	150 mg/dL	60 min	2.5MBq/kg	SUVmax	ROC curve	7.6		
Nakaigawa et al (2016)	6 h	150 mg/dL	1 h	2.5 MBq/kg	SUVmax	ROC curve	6.9		
Nakaigawaet al (2017)	6 h	150 mg/dL	1 h	2.5 MBq/kg	SUVmax	others	6.9		
Nakajima et al (2017)	5 h	200 mg/dL	75 min	3.5 MBq/kg	SUVmax MTV TLG	ROC curve	3.83	10.38	23.5
Namura et al (2010)	6 h	150 mg/dL	60 min	2.5MBq/kg	SUVmax	ROC curve	8.8		
Yoon et al (2013)	6 h	140 mg/dL	1 h	5.18MBq/kg	TLG	ROC curve			160
Pankowska et al (2018)	6 h	160 mg/dL	60 min	5–7MBq/kg	SUVmax	ROC curve	6.9		
Kayani et al (2011)	6 h	8 mmol/L	60 min	400 MBq	SUVmax		6.8		

MTV = metabolic tumor volume, NA = not available, ROC = receiver operating characteristic, SUVmax = maximum standard uptake value, TLG = total lesional glycolysis.

included in our meta-analysis[19–21,27–33] (Fig. 1). All 10 studies reported the prognostic value of SUVmax, MTV, or TLG in survival outcomes of patients with RCC.

3.2. Literature quality evaluation

The quality of the 10 included studies was assessed according to Critical Appraisal of Prognostic Studies (https://www.cebm.net/wp-content/uploads/2018/11/Prognosis.pdf) (Fig. 2). Generally, the studies were of high quality. In the domain of prognostic factor follow-up time measurements, high risk of bias was found in three studies owing to missing follow-up data or short follow-up times. Two non-blinded or non-randomized studies were evaluated as unclear risk of bias in the domain of defined representative sample measurements.

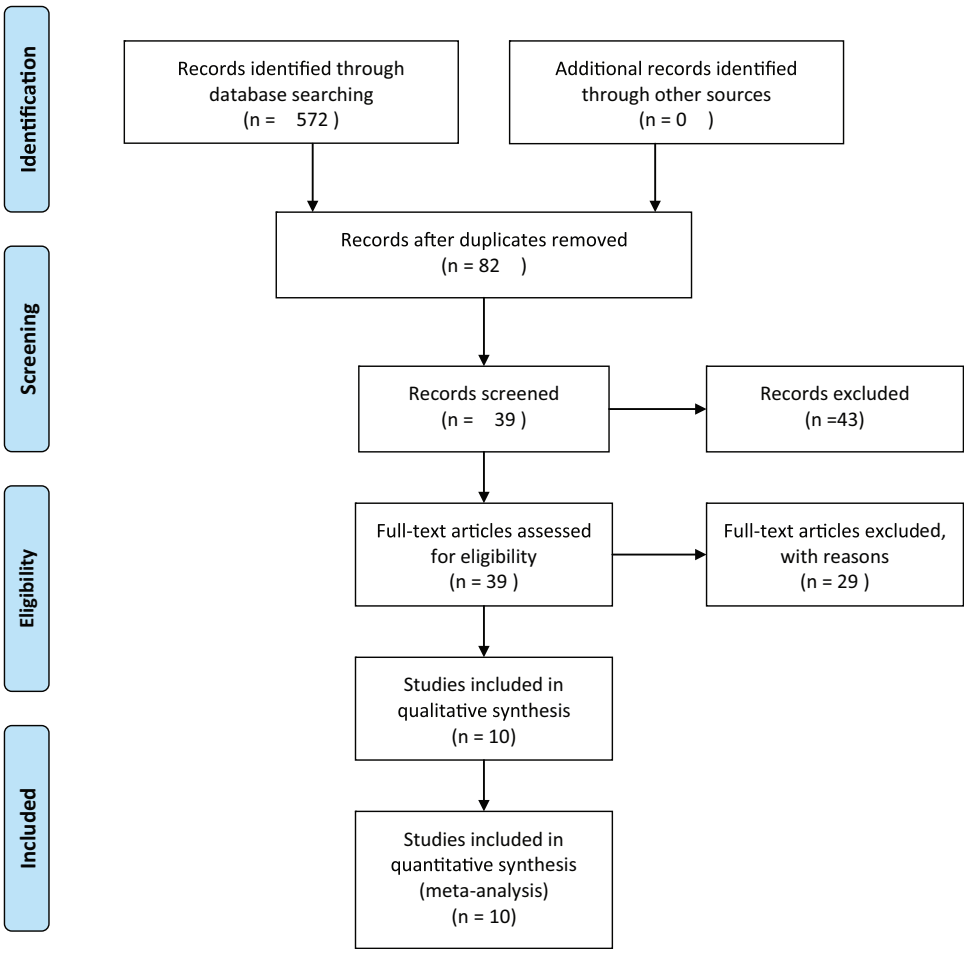

Figure 1. Flow diagram of study selection.

Figure 2. A, Risk of bias graph: Assessment of each risk of bias item presented as a percentage across all included studies. B, Risk of bias summary: Assessment of individual risk of bias items for each included study.

Adverse events were monitored using objective criteria in 9 of the studies.

3.3. Study characteristics

The majority of included studies were conducted in Asia (6 in Japan, 2 in South Korea, 1 in United States and 1 in Sweden). Four of the studies were prospective and 6 were retrospective. Among the nine studies assessing SUVmax, cut-off values ranged from 2.2 to 8.8, which included five items with EFS and 6 with OS as prognostic endpoints. The study of Hwang et al[21] included 2 sets of data with EFS and OS as prognostic endpoints. Among the 2 studies that measured MTV, both used EFS and one used OS as the primary endpoint. Two of the 3 studies measuring TLG assessed EFS and 2 evaluated OS. Additional information, such as age of subjects during the follow-up period of tumor pathological staging, was extracted. Six studies reported metastasis or recurrence of cancer. Moreover, 4 studies included a limited number of patients with primary lesions. The study of Kayani et al[31] was the only documented treatment of patients with clear cell pathology with Sunitinib. The other 9 studies included one or more treatments and histological features. The details of included studies, histology and treatments are presented in Table 1.

3.3.1. Primary outcome: EFS. Five investigations were included that analyzed EFS with SUVmax. We treated the study of Hwang et al[21] as 2 separate analyses since 2 sets of data on EFS with SUVmax were included in this case. After combining HR, higher SUVmax along with prediction of poorer EFS. The fixed-effects model (HR =1.32; 95% CI = 1.10–1.58, I^2 = 43.2%; P=.117) showed statistical significance (Fig. 3A) and no heterogeneity between the studies (Table 3). Funnel plots suggested risk of publication bias (Fig. 4A). Potential publication bias was further assessed using 2 statistical (Begg and Egger) tests. Neither Begg test (P=.060) nor Egger test (P=.848) showed evidence of significant publication bias (Fig. 4B). We also assessed sample size and mean age by logistic meta-regression analysis. Meta-regression analyses revealed that sample size (P=.434, Supplemental Fig. 1A, http://links.lww.com/MD/E132) and mean age (P=.118, Supplemental Fig. 1C, http://links.lww.com/MD/E132) did not produce the heterogeneity across studies.

Although there was no evidence of significant heterogeneity, subgroup analyses were further performed according to TNM staging, region, threshold, and analysis method (Table 4). The majority of studies including EFS as endpoint involved metastasis or recurrence of RCC, with a few including primary lesions. In studies on metastasis or recurrence of RCC, HR was estimated as 1.30 (95% CI: 1.08–1.56, I^2=49.7%, P=.093) and those on primary lesions showed no significant correlations (HR=2.30; 95% CI=0.8–8.69). Studies on regions in Asia had a HR of 1.39 (95% CI: 1.15–1.67, P=.008) and those in Europe showed no significant correlations (HR=0.43; 95% CI=0.18–1.02). According to the median SUVmax value, a threshold of 6.85 was selected and patients divided into high (≥6.85) and low (<6.85) subgroups. Subgroup meta-analyses illustrated that HRs of SUVmax have a high cut-off value of 1.34 (95% CI: 1.10–1.62, I^2=0%, P=.602). However, no significant correlations were

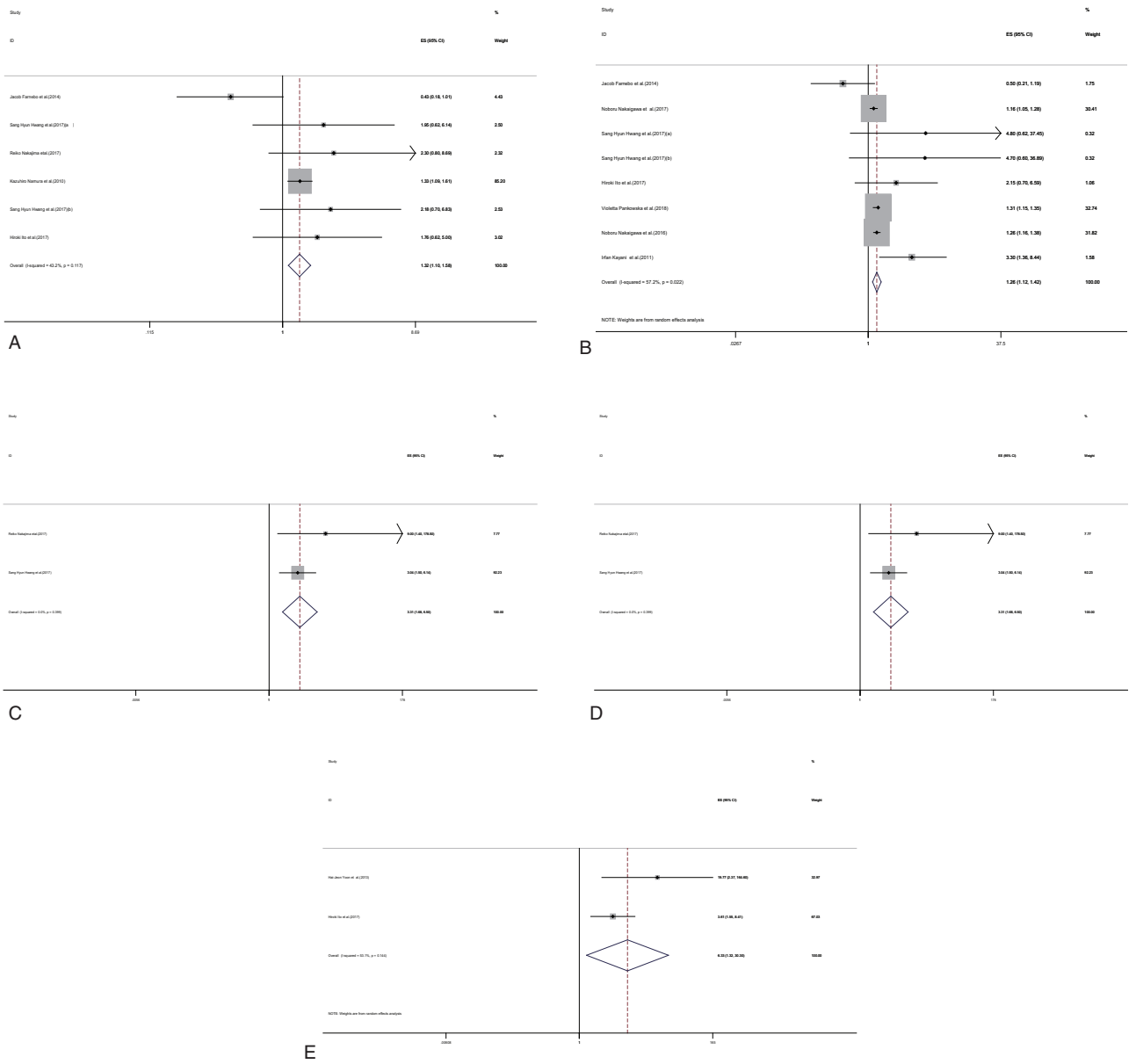

Figure 3. Forest plots of HR for EFS and OS with SUVmax (A, EFS; B, OS), metabolic tumor volume (C, OS) and TLG (D EFS; E, OS). Chi-squared test is a measurement of heterogeneity. $P < .05$ indicates significant heterogeneity (Squares = individual study point estimates. Horizontal lines = 95% CI. Rhombus = summarized estimate and its 95% CI. Fixed: fixed-effects model. Random: random effects model). EFS = event-free survival, OS = overall survival, SUVmax = maximal standard uptake value.

observed for HRs with low cut-off values (HR = 1.35; 95% CI = 0.55–3.30). In terms of analysis method, HR in multivariate analysis was 2.13 (95% CI = 1.07–4.17, $I^2 = 0\%$, $P = .980$). Univariate analysis disclosed no significant associations (HR = 1.03; 95% CI = 0.50–2.12). Based on study endpoint, eligible studies were classified into RFS, progression-free survival, and EFS groups. No significant results were obtained for all 3 groups.

EFS was analyzed in two studies on MTV and 2 on TLG. Data from comprehensive investigations showed association of poorer predicted EFS with higher MTV (HR = 2.40; 95% CI = 1.20–4.79, $I^2 = 26.5\%$; $P = .244$) (Fig. 3C) and TLG (HR = 3.31; 95% CI = 1.68–6.50, $I^2 = 0\%$; $P = .399$) (Fig. 3D), indicating that these parameters are significantly correlated with EFS. Due to the limited number of included studies, we did not conduct further publication bias and sensitivity analyses.

3.3.2. Primary outcome: OS. OS was based on seven studies evaluating SUVmax. The study of Hwang et al[21] included 2 sets of data and was therefore considered 2 separate studies. The fixed-effects model (HR = 1.258; 95% CI = 1.196–1.323, $I^2 = 57.2\%$; $P = .022$) (Fig. 3B, Table 3) disclosed statistical significance and heterogeneity between studies. Meaningful results were retained with the random-effects model (HR = 1.264; 95% CI = 1.124–1.421, $I^2 = 57.2\%$; $P = .022$). No significant publication bias was evident from Funnel plots (Fig. 4C). Begg test ($P = .902$) and Egger test ($P = .382$) (Fig. 4D)

Table 3

Summary of meta-analysis results.

Endpoint	Metabolic parameter	No. of studies	Model used	HR	95% CI of HR	*P* value of HR	Heterogeneity I^2 (%)	Conclusion
EFS	SUVmax	6	Fixed effect	1.32	1.10–1.58	.117	43.2	Significant
	MTV	2	Fixed effect	2.40	1.20–4.79	.244	26.5	Significant
	TLG	2	Fixed effect	3.31	1.68–6.50	.399	0	Significant
OS	SUVmax	8	Fixed effect	1.258	1.196–1.323	.022	57.2	Significant
			Random effect	1.264	1.124–1.421			Significant
	MTV	1	Fixed effect	3.52	1.451–8.536	–	–	Significant
	TLG	2	Fixed effect	4.56	2.08–10.00	.144	53.1	Significant
			Random effect	6.33	1.32–30.30			Significant

CI = confidence interval, EFS = event-free survival, HR = hazard ratios, MTV = metabolic tumor volume, OS = overall survival, SUVmax = maximum standard uptake value, TLG = total lesional glycolysis.

further showed no evidence of significant publication bias. Sensitivity analysis was conducted to further estimate the impact of combined HRs. Exclusion of individual studies did not induce significant changes, supporting the stability of the results. To explore the sources of heterogeneity across studies, we assessed sample size and mean age by logistic meta-regression analysis. Meta-regression analyses revealed that sample size ($P = .391$, Supplemental Fig. 1B, http://links.lww.com/MD/E132) and mean

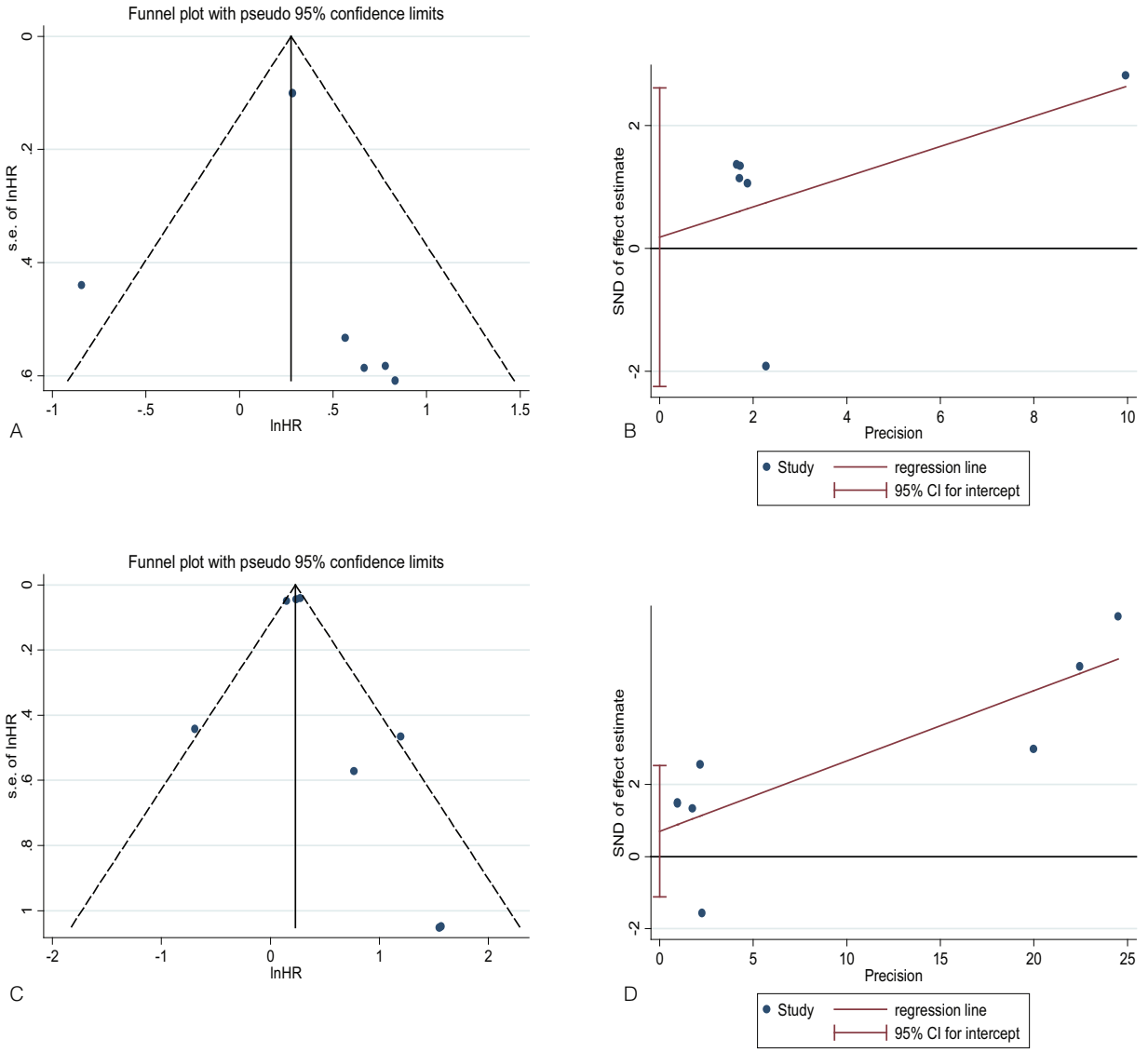

Figure 4. Funnel plots for EFS and OS with SUVmax (A, EFS; B, OS) and Egger test for EFS and OS with SUVmax (C, EFS; D, OS) The pseudo 95% confidence interval (CI) was computed as part of the analysis to produce the Funnel plots and corresponded to the expected 95% CI for a given standard error (SE). HR indicates hazard ratio. EFS = event-free survival, OS = overall survival, SUVmax = maximal standard uptake value.

Table 4

Subgroup of EFS and OS in relation to SUVmax.

Endpoint	Volumetric parameters	Factor	No. of studies	Heterogeneity test (I^2, P)	Effect model	HR	95%CI of HR	Conclusion
EFS	SUVmax	TNM staging						
		Metastasis or recurrence	5	49.7, .093	Fixed	1.30	1.08,1.56	Significant
		Included primary	1	–	–	2.30	0.8,8.69	Insignificant
		Region						
		Asian	5	0, .730	Fixed	1.39	1.15,1.67	Significant
		Europe	1	–	–	0.43	0.18,1.02	Insignificant
		Threshold						
		≥6.85	2	0, .602	Fixed	1.34	1.10,1.62	Significant
		<6.85	4	63.9, .040	Random	1.35	0.55,3.30	Insignificant
		Analysis method						
		Univariate analysis	3	69.8, .037	Random	1.03	0.50,2.12	Insignificant
		Multivariate analysis	3	0, .980	Fixed	2.13	1.07,4.17	Significant
		Endpoint						
		PFS	3	69.8, .037	Random	1.03	0.50,2.12	Insignificant
		RFS	2	0, .890	Fixed	2.06	0.92,4.64	Insignificant
		EFS	1	–	–	2.30	0.70, 7.58	Insignificant
OS	SUVmax	TNM staging						
		Metastasis or recurrence	6	50.2, .074	Random	1.21	1.04,1.41	Significant
		Included primary	2	74.3, .048	Random	1.85	0.77,4.44	Insignificant
		Region						
		Asian	6	35.3, .172	Fixed	1.26	1.20,1.32	Significant
		Europe	2	88.4, .003	Random	1.28	0.20,8.12	Insignificant
		Threshold						
		≥6.85	4	33.6, .211	Fixed	1.26	1.19,1.32	Significant
		<6.85	4	73.8, .010	Random	2.09	0.58,7.51	Insignificant
		Analysis method						
		Univariate analysis	2	75.4, .044	Random	0.99	0.24,4.12	Insignificant
		Multivariate analysis	6	55.1, .049	Random	1.27	1.15,1.41	Insignificant

CI = confidence interval, DFS = disease-free survival, EFS = event-free survival, HR = hazard ratios, MTV = metabolic tumor volume, OS = overall survival, PFS = progression-free survival, RFS = recurrence/relapse free survival, ROC = receiver operating characteristic, SUVmax = maximum standard uptake value, TLG = total lesional glycolysis.

age (P = .068, Supplemental Fig. 1D, http://links.lww.com/MD/E132) did not explain the heterogeneity across studies.

Additional subgroup analyses were performed according to TNM staging, region, and threshold (Table 4). The majority of studies that included OS as endpoint involved metastasis or recurrence of RCC, with a few including primary lesions. Studies with metastasis or recurrence of RCC had HR of 1.21 (95% CI: 1.04–1.41, I^2 = 50.2%, P = .074) and those that included primary lesions showed no significant correlations (HR = 1.85; 95% CI = 0.77–4.44). Studies on regions in Asia had HR of 1.26 (95% CI: 1.20–1.32, I^2 = 35.3%; P = .172) and those in Europe showed no significant correlations (HR = 1.28; 95% CI = 0.20–8.12). According to the median value of SUVmax, groups were divided into high (≥6.85) and low (<6.85) threshold subgroups. Subgroup meta-analyses illustrated that HR of SUVmax had a high cut-off value of 1.26 (95% CI: 1.19–1.32, I^2 = 33.6%, P = .211). However, no significant correlations were observed for HRs with low cut-off values (HR = 2.09; 95% CI = 0.58–7.51). Both multivariate (HR = 1.27; 95% CI = 1.15–1.41, I^2 = 55.1%; P = .049) and univariate analyses (HR = 0.99; 95% CI = 0.24–4.12, I^2 = 75.4%; P = .044) showed no significant associations.

OS was analyzed in one study on MTV (HR = 3.52; 95% CI = 1.451–8.536) and after combining HR of 2 studies on TLG (HR = 6.33; 95% CI = 1.32–30.30, I^2 = 53.1%; P = .144) (Fig. 3E; Table 3). The preliminary data indicate that MTV and TLG are significantly correlated with OS. Due to the limited number of included studies, we did not conduct further publication bias and sensitivity analyses.

4. Discussion

Clinical treatments for tumors, including renal cancer, are often not effective due to the lack of standard methods, highlighting the urgent medical need to reduce the side-effects of failed treatments and avoid unnecessary therapeutic efforts.[34] The potential significance of FDG uptake values in prognosis has recently been confirmed in several meta-analyses. High SUV values at diagnosis are highly associated with poor survival in a variety of cancer types, such as head-and-neck cancer, hepatocellular carcinoma, and bone and soft tissue sarcoma.[35–37] Volumetric parameters, such as MTV and TLG, additionally serve as prognostic factors in non-small cell lung cancer and head-and-neck cancer,[38,39] which may be of benefit to RCC patients if these parameters aid in predicting EFS and OS. ^{18}F-FDG-PET/CT may be applied for risk stratification in disease control and survival. However, the effectiveness of PET/CT for diagnosis of primary RCC remains a controversial issue. FDG PET is reported to play a limited role in diagnosis of primary RCC due to renal filtration of the radioisotope, which poses a challenge in differentiating renal masses from normal renal parenchyma.[40] A recent review by Karivedu et al[40] suggests that the efficacy of FDG PET in primary RCC is yet to be established and is not currently recommended for primary staging and initial diagnosis. However, the groups of Bachor[41] and Kumar[42] have demonstrated that FDG PET is effective in detecting primary RCC lesions. We did not exclude three studies incorporating primary lesions of RCC in our meta-analysis. The prognostic value of SUVmax,

MTV, and TLG of FDG PET/CT in patients with renal cancer was determined in terms of HR for EFS and OS. Upon pooling all 10 available studies, while SUVmax, MTV, and TLG were affected by various factors, higher values were associated greater risk of adverse events or death, compared with lower values. To our knowledge, this is the first meta-analysis to demonstrate the value of ^{18}F-FDG PET in mortality prediction in patients with solid RCC tumors.

No significant heterogeneity was found for SUVmax in EFS prediction (I^2=43.2%; P=.117). Furthermore, Begg test (P=.060) and Egger test (P=.848), revealed no significant publication bias. However, the association between SUVmax and survival outcomes may be affected by several confounding factors. We therefore conducted subgroup analysis according to TNM staging, region, threshold, and analysis method. Since the utility of FDG PET in primary RCC remains unclear and the method is not currently recommended for primary staging and initial diagnosis of RCC, TNM staging data were stratified into 2 subgroups. The subgroup with metastasis or recurrent RCC showed statistical significance and no heterogeneity while no significant correlations were observed for the group including primary lesions of RCC. In subgroup analyses performed according to region, threshold and analysis method, Asian location (I^2=0%, P=.73), threshold above 6.85 (I^2=0%, P=.602) and multivariate groups (I^2=0%, P=.980) showed statistical significance and no heterogeneity.

Significant heterogeneity was found for SUVmax in OS prediction. Begg test (P=.902) and Egger test (P=.382) revealed no significant publication bias. Sensitivity analyses supported the stability of the results. According to the guidelines and protocols for ^{18}F-FDG PET imaging, heterogeneity of PET/CT parameters (duration of fasting, preinjection blood glucose test, post-injection interval, and dose of ^{18}F-FDG) included in this study was acceptable as values were within the normal range[43–45] (Table 2). Meta-regression analyses also revealed that sample size and mean age did not explain the heterogeneity across studies. To investigate the source of heterogeneity, TNM stage, region, subgroup analysis was conducted according to threshold and analysis method (Table 3). The subgroup with metastasis or recurrence of RCC had HR of 1.21 (95% CI: 1.04–1.41, I^2=50.2%, P=.074) and showed statistical significance. Notably, no significant correlations were found for the group including primary lesions of RCC. In subgroup analyses performed according to region, threshold and analysis method, Asian location (I^2=35.3%; P=.172) and threshold above 6.85 (I^2=33.6%, P=.211) were considered homogeneous, leading to the conclusion that region and threshold are sources of heterogeneity for OS.

Our subgroup analysis demonstrated that SUVmax is a significant risk factor for both EFS and OS in RCC patient groups with metastasis or recurrence RCC. To our knowledge, the present meta-analysis is the first to confirm that high SUVmax presents a prognostic factor for outcome in RCC patients with metastasis or recurrence. No information on the association of SUVmax with survival for the group with primary lesions of RCC was available for systematic analysis. Due to the limited application of FDG PET in characterization of primary RCC, further studies are required to validate these findings.

Subgroup analysis further revealed that SUVmax is a significant risk factor for both EFS and OS in RCC patients of Asian origin. However, since only one European study analyzed EFS with SUVmax and 2 analyzed OS with SUVmax, the reliability of this finding may be affected by insufficient statistical power. Further research is warranted to validate the prognostic value of SUVmax in patients with RCC.

SUVmax was additionally identified as a significant risk factor for both EFS and OS in RCC patients with values above the median threshold of 6.85. However, we were unable to determine an optimal cut-off value of SUVmax. Different cut-off values and delineation strategies as well as histological methods used across the studies could affect the occurrence of events and survival. Further studies using data from individual patients are essential to determine the standard cut-off values and delineation methods for determining the survival predictive utility of SUVmax.

The volumetric parameters, MTV and TLG, could be utilized in metabolic analysis of radiotracer activity in tumor tissues to accurately reflect the tumor burden.[38,39] High values of volumetric parameters were associated with poor EFS and OS, suggesting that ^{18}F-FDG-PET/CT has significant utility in predicting survival outcomes of RCC patients. Owing to the lack of statistical data on MTV and TLG in relation to survival, systematic analysis was not possible, highlighting the requirement for further studies.

The quality of the included studies should also be taken into account as a limitation of our study. First, RCC is a heterogeneous disease and patients with different histological grades, stages, and treatments were included in our meta-analysis, which could affect the events occurring over time and survival. Moreover, very few patients with primary lesions of RCC were included and no studies evaluating the relationship between PET/CT parameters and survival in these cases were found, potentially leading to bias. Second, the included studies enrolled relatively small numbers of subjects (a total of 780 RCC patients). Third, although evaluation was performed using the Cochrane risk bias tool and included high-quality studies, some of the investigations partially lacked patient details and ^{18}F-FDG PET scan data. Fourth, non-English articles were excluded, and the potential impact of language bias cannot be overlooked. Fifth, only published studies were included when searching electronic databases, and therefore, the possibility of publication bias cannot be excluded. However, evaluation of publication bias supported the reliability of our data. Sixth, Engauge Digitizer was used to extract HR data from survival curves indirectly, which may lead to imprecision. Finally, the majority of studies included in this meta-analysis were conducted in Asia. Since the incidence of RCC is relatively high in these regions, race may contribute to bias (Supplemental document 1. , http://links.lww.com/MD/E134, Supplemental Table 1. , http://links.lww.com/MD/E135, Supplemental Figure 2, http://links.lww.com/MD/E133).

5. Conclusion

Despite the clinical heterogeneity of RCC patients and adoption of diverse methods among studies, data from our present meta-analysis confirm that high SUVmax is a significant prognostic factor for outcomes in patients with RCC, especially those with metastasis or recurring RCC. Additionally, MTV and TLG values were associated with prediction of higher risk of adverse events or death in patients with RCC. Further large-scale prospective studies are warranted to confirm the prognostic value of PET/CT parameters in RCC patients.

Author contributions

Conceptualization, Dongchun Xuan and Lan Liu; data curation, Weibo Wen, Shengri Tian and Dongyuan Xu; investigation, Dongyuan Xu and Weibo Wen; methodology, Dongchun Xuan,

Minhu Piao and Dongyuan Xu; writing—original draft, Dongchun Xuan, Weibo Wen, Shengri Tian; writing—review and editing, Dongchun Xuan, Weibo Wen, Shengri Tian, Minhu Piao, Dongyuan Xu, and Lan Liu.

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